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Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease (Review)

Poole P, Sathananthan K, Fortescue R

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Cochrane Database of Systematic Reviews 2019, Issue 5. Art. No.: CD001287.
DOI: 10.1002/14651858.CD001287.pub6.

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TABLE OF CONTENTS

[Intervention Review]

Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease

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Editorial group: Cochrane Airways Group.
Publication status and date: Edited (no change to conclusions), comment added to review, published in Issue 3, 2020.

Citation: Poole P, Sathananthan K, Fortescue R. Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2019, Issue 5. Art. No.: CD001287. DOI: 10.1002/14651858.CD001287.pub6.

ABSTRACT

Background

Individuals with chronic bronchitis or chronic obstructive pulmonary disease (COPD) may suffer recurrent exacerbations with an increase in volume or purulence of sputum, or both. Personal and healthcare costs associated with exacerbations indicate that therapies that reduce the occurrence of exacerbations are likely to be useful. Mucolytics are oral medicines that are believed to increase expectoration of sputum by reducing its viscosity, thus making it easier to cough it up. Improved expectoration of sputum may lead to a reduction in exacerbations of COPD.

Objectives

Primary objective

• To determine whether treatment with mucolytics reduces exacerbations and/or days of disability in patients with chronic bronchitis or COPD

Secondary objectives

• To assess whether mucolytics lead to improvement in lung function or quality of life

• To determine frequency of adverse effects associated with use of mucolytics

Search methods

We searched the Cochrane Airways Group Specialised Register and reference lists of articles on 12 separate occasions, most recently on 23 April 2019.

Selection criteria

We included randomised studies that compared oral mucolytic therapy versus placebo for at least two months in adults with chronic bronchitis or COPD. We excluded studies of people with asthma and cystic fibrosis.

Data collection and analysis

This review analysed summary data only, most derived from published studies. For earlier versions, one review author extracted data, which were rechecked in subsequent updates. In later versions, review authors double-checked extracted data and then entered data into RevMan 5.3 for analysis.

Main results

We added four studies for the 2019 update. The review now includes 38 trials, recruiting a total of 10,377 participants. Studies lasted between two months and three years and investigated a range of mucolytics, including N-acetylcysteine, carbocysteine, erdosteine, and ambroxol, given at least once daily. Many studies did not clearly describe allocation concealment, and we had concerns about blinding and high levels of attrition in some studies. The primary outcomes were exacerbations and number of days of disability.

Results of 28 studies including 6723 participants show that receiving mucolytics may be more likely to be exacerbation-free during the study period compared to those given placebo (Peto odds ratio (OR) 1.73, 95% confidence interval (CI) 1.56 to 1.91; moderate-certainty evidence). However, more recent studies show less benefit of treatment than was reported in earlier studies in this review. The overall number needed to treat with mucolytics for an average of nine months to keep an additional participant free from exacerbations was eight (NNTB 8, 95% CI 7 to 10). High heterogeneity was noted for this outcome (I^2 = 62%), so results need to be interpreted with caution. The type or dose of mucolytic did not seem to alter the effect size, nor did the severity of COPD, including exacerbation history. Longer studies showed smaller effects of mucolytics than were reported in shorter studies.

Mucolytic use was associated with a reduction of 0.43 days of disability per participant per month compared with use of placebo (95% CI -0.56 to -0.30; studies = 9; I^2 = 61%; moderate-certainty evidence). With mucolytics, the number of people with one or more hospitalisations was reduced, but study results were not consistent (Peto OR 0.68, 95% CI 0.52 to 0.89; participants = 1788; studies = 4; I^2 = 58%; moderate-certainty evidence). Investigators reported improved quality of life with mucolytics (mean difference (MD) -1.37, 95% CI -2.85 to 0.11; participants = 2721; studies = 7; I^2 = 64%; moderate-certainty evidence). However, the mean difference did not reach the minimal clinically important difference of -4 units, and the confidence interval includes no difference. Mucolytic treatment was associated with a possible reduction in adverse events (OR 0.84, 95% CI 0.74 to 0.94; participants = 7264; studies = 24; I^2 = 46%; moderate-certainty evidence), but the pooled effect includes no difference if a random-effects model is used. Several studies that could not be included in the meta-analysis reported high numbers of adverse events, up to a mean of five events per person during follow-up. There was no clear difference between mucolytics and placebo for mortality, but the confidence interval is too wide to confirm that treatment has no effect on mortality (Peto OR 0.98, 95% CI 0.51 to 1.87; participants = 3527; studies = 11; I^2 = 0%; moderate-certainty evidence).

Authors' conclusions

In participants with chronic bronchitis or COPD, we are moderately confident that treatment with mucolytics leads to a small reduction in the likelihood of having an acute exacerbation, in days of disability per month and possibly hospitalisations, but is not associated with an increase in adverse events. There appears to be limited impact on lung function or health-related quality of life. Results are too imprecise to be certain whether or not there is an effect on mortality. Our confidence in the results is reduced by high levels of heterogeneity in many of the outcomes and the fact that effects on exacerbations shown in early trials were larger than those reported by more recent studies. This may be a result of greater risk of selection or publication bias in earlier trials, thus benefits of treatment may not be as great as was suggested by previous evidence.

PLAIN LANGUAGE SUMMARY

Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Background to the question

Chronic obstructive pulmonary disease (COPD) and chronic bronchitis are long-term breathing conditions. They cause symptoms such as shortness of breath, cough, and excess sputum. People with COPD and chronic bronchitis may have flare-ups (exacerbations) when their symptoms become worse.

Mucolytics are medicines taken orally that may loosen sputum, making it easier to cough it up. Mucolytics may have other beneficial effects on lung infection and inflammation and may reduce the number of flare-ups that people with COPD and chronic bronchitis have. Mucolytics can also be inhaled, but we did not look at inhaled mucolytics in this review.

Study characteristics

We looked for studies lasting at least two months, in which it was decided at random whether a person received a mucolytic drug or a placebo. We did not include studies involving children or people with other breathing conditions such as asthma and cystic fibrosis.

We found 38 studies to include in our review. These studies included a total of 10,377 adults with COPD or chronic bronchitis. The studies used a variety of mucolytic drugs, including N-acetylcysteine, carbocysteine, and erdosteine and lasted from two months to three years. Mucolytics were taken by mouth between one and three times per day. These studies measured several different outcomes to find out if the drug was useful, including flare-ups, hospital admissions, quality of life, lung function, and side effects.

Key results

We found that people taking mucolytic drugs were less likely to experience a flare-up compared to those taking placebo. Approximately eight people would need to take the drug for nine months for one extra person to avoid having a flare-up. This result was based on 28

studies involving 6723 people. However, the studies carried out a longer time ago (1970s to 1990s) show greater benefit than those carried out more recently. Shorter studies also seemed to show more benefit than longer studies. This could be because the newer trials were larger and may be showing that mucolytics are less beneficial than the earlier studies showed. Or it could be that only studies that showed mucolytics as beneficial were published before the 2000s, when there was a push to report all trial results regardless of whether or not they showed benefit.

People taking mucolytics had fewer days of disability (i.e. days when they could not do their normal activities) every month, but this was quite a small difference - less than half a day per person per month. They were also approximately one-third less likely to be admitted to hospital, although this result is based on only five studies that provided this information.

Study results suggest that mucolytics do not have an important impact on quality of life or lung function. People taking mucolytics did not experience more unwanted side effects than those taking placebo. But we could not be sure about their impact on death during the study period because only 37 deaths occurred amongst the 3527 participants in studies where deaths were measured and reported.

Quality of the evidence

We are moderately confident about the results we have presented. Our confidence is reduced by the results from individual studies looking quite different from one another and the mix of older and newer studies that we found. Also, in some cases there were not enough data to be sure whether mucolytics were better or worse than, or the same as, placebo.

Conclusions

Mucolytics appear to be useful for reducing flare-ups, days of disability, and hospital admissions in people with COPD or chronic bronchitis, and they do not appear to cause more side effects. However, they do not appear to have much impact on quality of life or lung function, and we could not be sure about their impact on death.

This plain language summary is current to April 2019.

Summary of findings for the main comparison. Mucolytic compared to placebo for chronic bronchitis or chronic obstructive pulmonary disease

Mucolytic compared to placebo for chronic bronchitis or chronic obstructive pulmonary disease

Patient or population: chronic bronchitis or COPD
Setting: community
Intervention: mucolytic
Comparison: placebo

Outcomes*	Anticipated absolute effects† (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with mucolytic				
Participants with no exacerbations in study period Follow-up: 8.8 months	386 per 1000	521 per 1000 (495 to 545)	Peto OR 1.73 (1.56 to 1.91)	6723 (28 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	Generally larger effects in earlier studies of mucolytics in chronic bronchitis and smaller effects in more recent studies in COPD
Days of disability per participant per month Follow-up: 8.3 months	Mean days of disability per participant per month was 1.57 days	MD 0.43 days lower (0.56 lower to 0.30 lower)	-	2259 (9 RCTs)	⊕⊕⊕⊖ **Moderate**[a,b]	
Health-related quality of life (total score SGRQ) Scale from 1 to 100; lower scores indicate better quality of life Follow-up: 14.1 months	Mean SGRQ total score was 39.02 points	MD 1.37 lower (2.85 lower to 0.11 higher)	-	2721 (7 RCTs)	⊕⊕⊕⊖ **Moderate**[a,c]	MCID for SGRQ is 4 points
Hospitalisation during study period Follow-up: 16.6 months	188 per 1000	136 per 1000 (107 to 171)	Peto OR 0.68 (0.52 to 0.89)	1833 (5 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	
FEV_1 at end of study Follow-up: 14.5 months	Mean FEV_1 at end of study was 1.50 L	MD 0.04 L higher (0.01 higher to 0.07 higher)	-	3473 (14 RCTs)	⊕⊕⊕⊖ **Moderate**[a,b]	MCID for FEV_1 in COPD is approximately 0.1 L (Jones 2013)

Adverse effects Follow-up: 8.2 months	235 per 1000	205 per 1000 (185 to 224)	Peto OR 0.84 (0.74 to 0.94)	7264 (24 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	
Death during study period Follow-up: 13.3 months	11 per 1000	10 per 1000 (5 to 20)	Peto OR 0.98 (0.51 to 1.87)	3527 (11 RCTs)	⊕⊕⊕⊖ **Moderate**[d]	18 deaths on mucolytics and 19 on placebo

*Follow-up was calculated as a weighted mean duration.
†**The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second; MCID: minimally clinically important difference; MD: mean difference; OR: odds ratio; RCT: randomised controlled trial; RR: risk ratio; SGRQ: St. George's Respiartory Questionaire; WMD: weighted mean duration.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Statistical and clinical heterogeneity identified. Downgraded once for inconsistency.
[b]Funnel plots suggest small negative trials under-represented (Figure 1; Figure 2). However, removing the positive small trials from the analysis had little impact on the pooled estimate. No downgrade.
[c]Confidence interval includes possibility of no difference between groups, but both ends of confidence interval lie within MCID. No downgrade for imprecision.
[d]Confidence interval includes possibility of both an important increase or reduction in deaths. Downgraded once for imprecision.

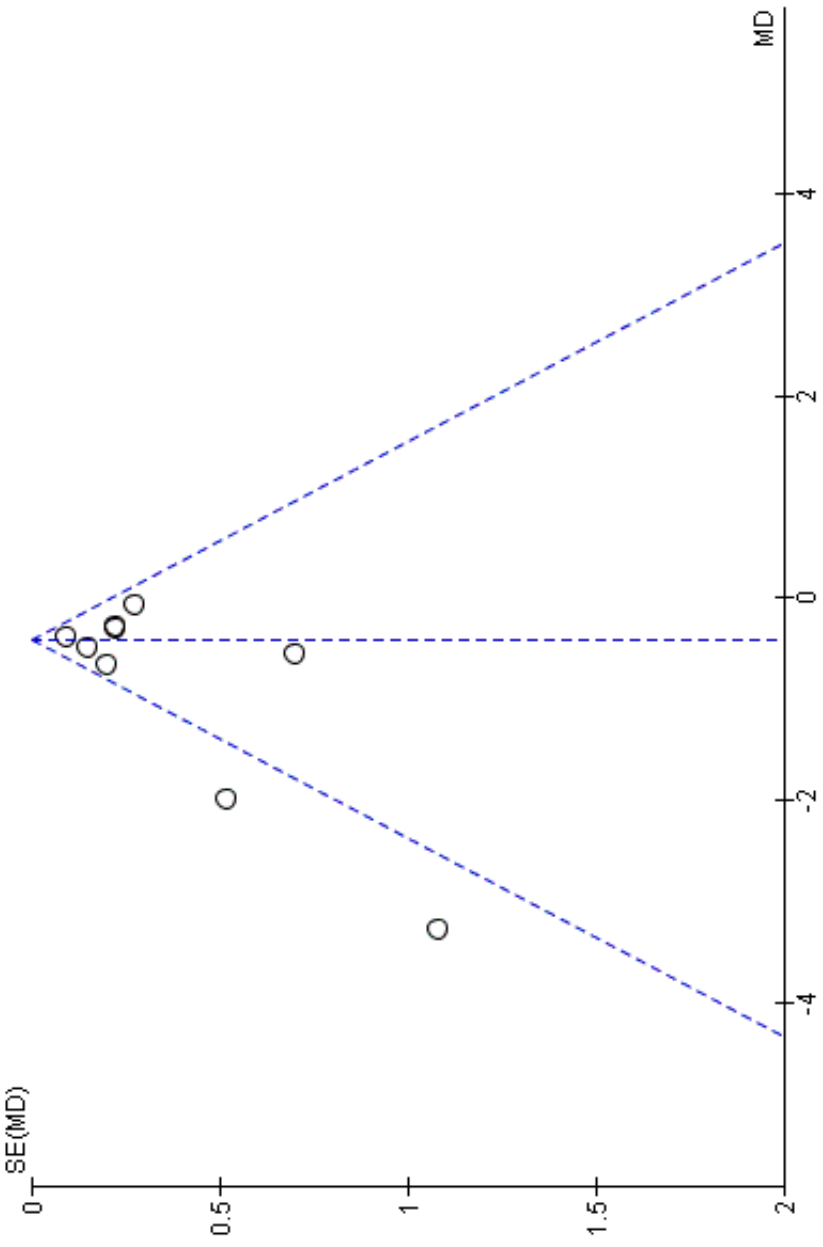


Figure 1. Funnel plot of comparison: 1 Mucolytic versus placebo, outcome: 1.11 Days of disability per participant per month.

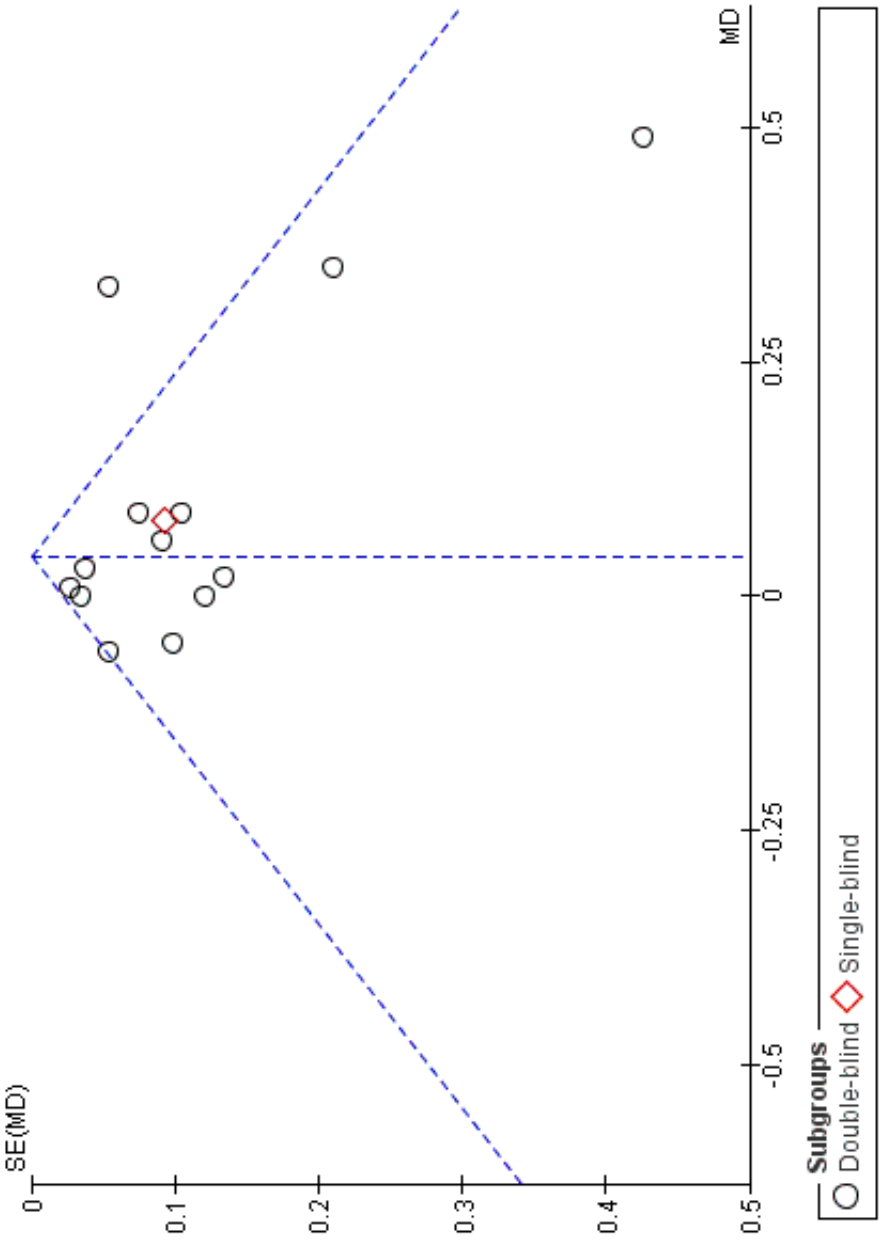


Figure 2. Funnel plot of comparison: 1 Mucolytic versus placebo, outcome: 1.13 FEV_1 at end of study.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is a long-term progressive condition primarily affecting the lungs, but with a wide range of extrapulmonary manifestations. Symptoms typically include shortness of breath (dyspnoea), impaired exercise tolerance, wheezing, cough, and sputum production. In more severe cases, COPD may progress to cor pulmonale, respiratory failure, and death (Qaseem 2011). It is estimated that COPD is the fourth most common single cause of death worldwide (WHO 2017). Few interventions have been demonstrated to convincingly reduce mortality, with the exception of smoking cessation, long-term oxygen therapy in hypoxaemic patients and lung volume reduction surgery in selected patients (GOLD 2019; van Agteren 2016).

A diagnosis of COPD is usually made when a person who has symptoms of COPD is found to have airflow obstruction (post-bronchodilator forced expiratory volume in one second (FEV_1)/ forced vital capacity (FVC) < 0.70) in the absence of an alternative explanation for the symptoms (e.g. left ventricular failure) or the airflow obstruction (e.g. asthma) (Qaseem 2011). Many people with chronic bronchitis also have COPD. Smoking is the main risk factor for COPD; up to 50% of smokers will develop COPD, and most will have some breathing impairment (GOLD 2019; Rennard 2006). Chronic bronchitis and COPD are preventable and treatable diseases that are associated with an enhanced chronic inflammatory response to noxious particles or gases in the airways and the lung (GOLD 2019). Exacerbations and comorbidities contribute to overall severity in individual patients.

Exacerbations occur with increasing frequency as the disease becomes more severe. They are characterised by increased breathlessness or greater volume or purulence of sputum, or both. Exacerbations accelerate decline in lung function and are associated with worse quality of life and higher mortality. They are the largest contributor to healthcare costs in COPD (Criner 2015). Thus, treatments that reduce the frequency and duration of acute exacerbations will provide benefit for both individual patients and healthcare systems.

Description of the intervention

Mucolytics are oral medicines, given at least once daily, that are believed to increase expectoration of sputum by reducing its viscosity, thus making it easier to cough it up. There are several different types of mucolytic, including carbocysteine, acetylcysteine, erdosteine, and ambroxol (Yang 2018). They are given in combination with, rather than instead of, other COPD therapies, such as inhaled long-acting $beta_2$-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs).

Mucolytics are included as a treatment option for patients experiencing frequent exacerbations in several national and international management guidelines. International Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines state that mucolytics may reduce exacerbations and modestly improve health status, but there is currently a lack of evidence to precisely target the population most likely to benefit (GOLD 2019). COPD-X guidelines, produced in Australia and New Zealand, give a stronger recommendation, stating "there is evidence to support the use of high dose oral N-acetylcysteine in the reduction of COPD exacerbations and improvements in lung function" and "high dose (≥ 1200 mg/day) N-acetylcysteine should be considered as an effective therapy for reducing exacerbations" (Yang 2018). UK National Institute for Health and Care Excellence (NICE) guidelines currently suggest that mucolytics should be considered for patients with chronic cough productive of sputum and continued if there is symptomatic improvement. However, the guidelines state they should not be routinely prescribed to prevent exacerbations (NICE 2018). Joint American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines for prevention of exacerbations make the following recommendation: "for patients who have COPD with moderate or severe airflow obstruction and exacerbations despite optimal inhaled therapy, we suggest treatment with an oral mucolytic agent to prevent future exacerbations" (Wedzicha 2017). However, this is qualified as being a conditional recommendation, based on low quality of evidence.

How the intervention might work

Mucus clearance is one of the most important tools the lung has to protect itself from pathogens (Rubin 2014). Mucus is a gel-like material complete with glycoproteins called mucins, serum proteins, and water. In contrast, sputum refers to expectorated mucus with the addition of inflammatory cells and DNA. Mucus is removed from the lungs and airways via cilia hairs and airflow; however sputum is removed primarily by coughing (Rubin 2014).

Mucolytics work by changing the physical properties of the secretions themselves. They can work by degrading the mucin polymers, fibrin, or DNA in airway secretions, which makes them less viscous. This makes it easier for the body to clear them and reduces the risk of bacterial contamination. Classic mucolytics such as N-acetylcysteine (NAC) exert their effects by depolymerising the mucin glycoproteins via a hydrolysis reaction (Rubin 2007). One study found that NAC may improve pulmonary function, but there was uncertainty as to whether or not this was in fact mediated by its antioxidant ability (Hansen 1994). Given that oxidative stress is thought to be an amplifying mechanism in COPD (Rahman 2005), this property of N-acetylcysteine may be useful in chronic airways disease.

Lubricants and surfactant stimulators such as ambroxol can make the sputum less adhesive, making it easier for the cilia to clear and more likely that a cough will be able to transport it throughout the pharynx (Rubin 2007). In a chronic inflammatory process such as COPD, production of phospholipase A2 can cause destruction of the surfactant phospholipids, making the sputum incredibly adherent to the cilia and further causing airway obstruction (Rubin 2007). One study found that aerosolised surfactant was able to increase FEV_1 % predicted and FVC by up to 10% by reducing adherence of mucus in the airways (Anzueto 1997).

Why it is important to do this review

As illustrated by varied recommendations from guidelines, there is lack of international consensus on the place of mucolytics in the treatment of COPD. As theoretical reasons have been proposed to explain why mucolytics may work in both chronic bronchitis and COPD, and because treatments that reduce exacerbations are needed to reduce morbidity and costs, this review update will seek to determine the true effect of this class of medicines.

OBJECTIVES

Primary objective

- To determine whether treatment with mucolytics reduces exacerbations and/or days of disability in patients with chronic bronchitis or COPD

Secondary objectives

- To assess whether mucolytics lead to improvement in lung function or quality of life
- To determine the frequency of adverse effects associated with use of mucolytics

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised, placebo-controlled trials.

Types of participants

We included studies of adults (over 20 years of age) with chronic bronchitis as defined by the British Medical Research Council (cough and sputum on most days during at least three consecutive months for longer than two successive years) or COPD as defined by the criteria of the American Thoracic Society, the Global Initiative for Chronic Obstructive Lung Disease (GOLD), the European Respiratory Society, or the World Health Organization (WHO). We excluded studies on patients with asthma or cystic fibrosis.

Types of interventions

Participants must have received regular treatment with oral mucolytics or placebo for at least two months. Oral mucolytics included the following compounds: N-acetylcysteine (NAC), S-carboxymethylcysteine, bromhexine, ambroxol, erdosteine, sobrerol, cithiolone, letosteine, iodinated glycerol, N-isobutyrylcysteine, myrtol, and cineole.

We excluded studies of inhaled mucolytics and combinations of mucolytics with antibiotics and mucolytics with bronchodilators, as well as studies of deoxyribonuclease or proteases such as trypsin.

Types of outcome measures

Primary outcomes

- Exacerbations, as measured by the number of participants with no exacerbations during the study period, as well as the total number of acute exacerbations per participant* and time to first exacerbation. Exacerbation was defined as an increase in cough and by volume and/or purulence of sputum
- Number of days of disability variously defined as days in bed, days off work, or days on which the participant was unable to undertake normal activities. We also assessed days on antibiotics

*For the 2019 update, we removed exacerbations per patient per month analyses as these are not considered to be as statistically robust as the dichotomous exacerbation outcome, largely due to likely skew in this measure. Instead we present these data in tables.

Secondary outcomes

- Measures of lung function, including forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and peak expiratory flow rate (PEFR)
- Adverse effects of treatment
- Hospitalisation and mortality
- Quality of life as measured by a tool validated in patients with COPD

We had intended to use symptom scores as a secondary outcome measure, but it became clear that symptoms were not reported in a consistent fashion, and it was not possible to standardise symptom scores.

Adverse events were not usually reported in detail and generally were mild and self-limiting, so we have entered only the total number of adverse events.

Search methods for identification of studies

Electronic searches

Search methods and search history for previous versions of this review are detailed in Appendix 1. The previously published version included searches up to July 2014. The search period for this update is July 2014 through April 2019.

We identified studies from the Cochrane Airways Group Trials Register (CAGR), which is maintained by the Information Specialist for the Group. The Cochrane Airways Trials Register contains studies identified from several sources.

- Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies (CRS).
- Weekly searches of MEDLINE Ovid.
- Weekly searches of Embase Ovid.
- Monthly searches of PsycINFO Ovid.
- Monthly searches of Cumulative Index to Nursing and Allied Health Literature (CINAHL) EBSCO.
- Handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register are identified through search strategies based on the scope of Cochrane Airways. Details of these strategies, as well as a list of handsearched conference proceedings, are provided in Appendix 2. We searched for relevant trials in the Register using the search strategy presented in Appendix 3. We did not apply restrictions on language or type of publication.

Searching other resources

We checked the references of all papers and reviews for which we obtained the full text to identify other relevant articles. We asked other researchers in the field to provide additional references, and we remained open to unsolicited suggestions regarding potentially eligible studies. For the 2014 and 2019 updates, we searched these online clinical trials registers: ClinicalTrials.gov (www.ClinicalTrials.gov) and the WHO trials portal (www.who.int/ictrp/en/).

Data collection and analysis

Selection of studies

At least one review author (Peter Black and PP for original review; PP and Jimmy Chong for the 2001, 2006, and 2012 updates; and PP and RF for the 2019 update) assessed all abstracts obtained from the search of the CAGR. We obtained the full text for those that appeared to fit the criteria for inclusion (or if this was not clear from the abstract). Two review authors independently selected trials for inclusion in the original review and updates and resolved disagreements over inclusion by discussion. Six translators (two of whom were medically trained) assessed papers published in languages other than English. For the 2012 and 2014 updates, the review lead author (PP) was assisted by another Cochrane review author (Jimmy Chong) in extracting data. For the 2019 update, RF and KS extracted and entered data, with input from PP.

Data extraction and management

We extracted data onto worksheets before entering them into the Review Manager software (RevMan 5.3). We double-checked all entries against the original paper. In the 1999 update, we rechecked all data from earlier studies. In the 2019 update, we rechecked lung function data from earlier studies to separate the analyses into FEV_1, percent predicted FEV_1, PEFR, and FVC, rather than a combined standardised mean difference analysis.

Assessment of risk of bias in included studies

We used the following to assess sources of bias in selection, allocation, performance, detection, attrition, or reporting (Higgins 2011).

- Low risk of bias.
- Unclear risk of bias: if insufficient information was available.
- High risk of bias.

When assessing attrition bias, we used an approximate cut-off of 20% dropout for high risk, although we also took into account the type of analysis performed (e.g. intention-to-treat), the balance between trial arms, and the reasons given for dropout.

Measures of treatment effect

We analysed continuous data using mean differences (MDs). We used Peto odds ratios (ORs) for dichotomous data and reported results with 95% confidence intervals (CIs).

Unit of analysis issues

We calculated exacerbation rates and days of disability by dividing the number of events by the number of participants and the number of months of the study (i.e. per participant per month). We scaled standard deviations for monthly rates in the same way. For the 2019 update, we archived the exacerbation rates analyses.

Dealing with missing data

If data were insufficient, we requested further information by writing to the study author or to the pharmaceutical company sponsoring the study.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. We reported cases of substantial heterogeneity and explored possible causes by performing prespecified subgroup analysis. As per the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we considered the following ranges for assessing heterogeneity.

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: may show considerable heterogeneity.

Assessment of reporting biases

When we were able to pool more than 10 trials, we created and examined a funnel plot to explore possible small-study and publication biases.

Data synthesis

We used summary statistics rather than individual patient data. We used a fixed-effect model.

For the outcome of having 'no exacerbation in the study period', we calculated a number needed to treat for an additional beneficial outcome (NNTB) based on the pooled Peto odds ratio (Cates 2002), with baseline risk taken from the pooled control group event rate (total number of events divided by overall number of participants in the placebo group multiplied by 100).

Subgroup analysis and investigation of heterogeneity

From the outset, we planned a priori subgroup analyses based on type of mucolytic, dose, duration, country of study, disease severity, and whether or not participants were included, as they had a history of exacerbation.

Following publication of the BRONCUS study (Decramer 2005), which suggested a differential effect of mucolytics depending on concomitant treatment, we included an analysis on whether concomitant inhaled corticosteroids were permitted.

From 2012 onwards, we carried out a post hoc investigation of time trends in data for participants with one or more exacerbations by comparing results of trials published since 2000 versus those published earlier.

Sensitivity analysis

For 2012 onwards, we explored heterogeneity in results on exacerbations, and we conducted a sensitivity analysis using data from trials assessed as having low risk of selection bias (on the basis of allocation concealment). For the 2019 update, we conducted a sensitivity analysis removing studies judged to be at high risk of attrition bias.

RESULTS

Description of studies

Results of the search

For details of the search history, see Appendix 1, and for the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) study flow diagram for this update, see Figure 3.

Figure 3. Study flow diagram: review update.

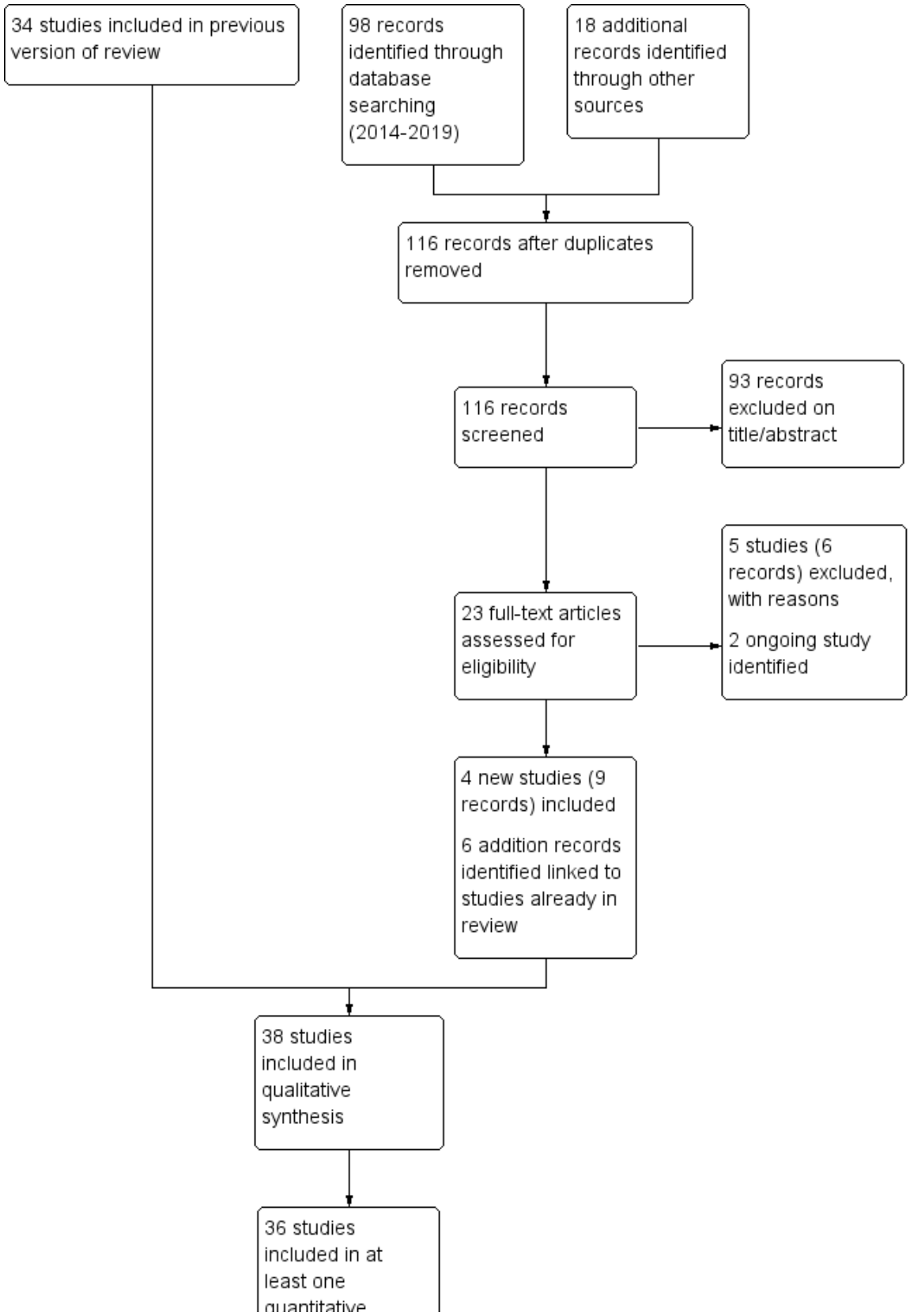
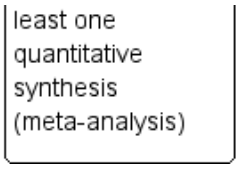


Figure 3. (Continued)



After de-duplication, the database search run on 23 April 2019 yielded 98 references, and searches of clinical trial registries identified a further 18 records. We excluded 93 on the basis of title and abstract and reviewed 23 full texts for possible inclusion. We excluded a further six records (five unique studies) at this stage and identified two ongoing studies that meet the inclusion criteria for this review (Characteristics of ongoing studies). The remaining 15 records were eligible for inclusion. We added nine records, linked to four new unique studies, to the review (Dal Negro 2017; Fukuchi 2016; Johnson 2016; Xu 2014). We identified a further six records, which were additional references to studies already included in the review. We wrote to authors of all four newly included studies to request further information; we received a response from the authors of Dal Negro 2017, Fukuchi 2016, and Johnson 2016, and we are grateful to Professor Dal Negro, Professor Inoue, and Dr Niewoehner for the additional data/details they provided.

The 2014 search yielded 29 abstracts, as well as four new eligible studies - all of NAC versus placebo. Four abstracts related to the eligible study of Zheng 2014, four to Tse 2013, three to De Backer 2013, and one to Roy 2014. We found a total of 17 reports of ineligible studies, including Moretti 2011, which in 2012 was awaiting classification. We found a further report of the Roy study while searching for study authors' contact details. Searches of online clinical trials databases yielded no further studies.

In the initial review in 1997, we wrote to the authors of 10 studies (Allegra 1996; Babolini 1980; Boman 1983; Castiglioni 1986; Christensen 1971; Grillage 1985; Jackson 1984; Nowak 1999; Parr 1987; Petty 1990) to request more information. We received further data for two studies (Allegra 1996; Nowak 1999). Dr Petty responded to our letter but could not supply data because they were held by a pharmaceutical company (the company has not replied to two letters). Dr Boman wrote to say that he was unable to supply us with additional data. This was also the case for Novartis Pharmaceuticals (UK), which responded on behalf of two study authors (Jackson 1984; Parr 1987), and Parke Davis Research Laboratories (Grillage 1985). We received no reply to our request for additional data related to the remaining three studies (Babolini 1980; Castiglioni 1986; Christensen 1971), although we sent two letters. We also wrote to the authors of Olivieri 1987 to clarify the error measurement used, but we received no reply. Pharmaceutical companies notified us of two studies (Meister 1986; Meister 1999); the former was unpublished. They also provided further information on four studies (Meister 1986; Meister 1999; Nowak 1999; Pela 1999). In 2008 we contacted an author of the COOPT study, 'A double-blind placebo-controlled trial comparing the efficacy and cost-effectiveness of inhaled fluticasone propionate versus oral N-acetylcysteine in the treatment of patients with COPD in general practice' (Clinical Trials identifier: NCT00184977), which was conducted from 1998 to 2003, to ascertain whether any data might be made available for this review. This study has now been published and is included in the review (Schermer 2009). In 2012, we contacted the lead author of Decramer 2005 to clarify conflicting information on quality of life in the published report; the lead author helpfully provided us with information derived from the St George's Respiratory Questionnaire (SGRQ).

In 2014, we wrote to Dr De Backer to request additional details on the secondary outcomes of spirometry and quality of life (De Backer 2013), but we received no response. As this was a small cross-over study with few outcomes of relevance to this review, we have not pursued this. Dr Zheng provided the appendix to Zheng 2014, which contained further details on study design and outcomes. In response to another request, Dr Zheng provided standard deviations (SDs) of exacerbation rates and total SGRQ, as well as mean (SD) end of study FEV_1 and FVC values.

Included studies

By 2019, this review included 38 randomised controlled trials (RCTs), which had recruited a total of 10,377 participants. We provide full details of each study in Characteristics of included studies and an overview in Table 1.

A total of 15 studies examined use of mucolytics in people with COPD only (Bachh 2007; Dal Negro 2017; De Backer 2013; Decramer 2005; Fukuchi 2016; Malerba 2004; Moretti 2004; Nowak 1999; Pela 1999; Roy 2014; Tse 2013; Worth 2009; Xu 2014; Zheng 2008; Zheng 2014). The other studies involved people with chronic bronchitis, COPD, or both.

All but four studies were randomised, double-blind, and placebo-controlled and used a parallel-group design. Blinding was not described in Xu 2014. Study duration ranged from 2 to 36 months. Fourteen studies had a run-in period (Allegra 1996; Boman 1983; Dal Negro 2017; Ekberg-Jansson 1999; Fukuchi 2016; Malerba 2004; McGavin 1985; Meister 1999; Moretti 2004; Olivieri 1987; Schermer 2009; Tse 2013; Zheng 2008; Zheng 2014). Four studies were described as randomised and placebo-controlled but not as double-blind. One of these was labelled as 'open' (Pela 1999), and two (Bachh 2007; Roy 2014) were 'single-blind' trials. The fourth was a randomised cross-over trial (De Backer 2013). As a result of the potential for bias, these are reported separately in analyses of primary outcomes.

In one study conducted in primary care practices (Schermer 2009), investigators compared NAC 600 mg daily versus placebo as well as inhaled fluticasone 500 µg twice daily in a three-arm study of double-dummy design. This review used data from NAC and placebo arms only.

Inclusion and exclusion criteria

All studies indicated that participants fulfilled criteria for chronic bronchitis, COPD, or both (except Nowak 1999, which has been published in abstract form only). Exclusion criteria varied, and

some studies did not report whether patients with other respiratory illnesses were excluded.

Lung function

All but two studies - Grassi 1976 and Parr 1987 - reported baseline lung function using PEFR, FEV_1 or FEV_1 % predicted. When studies reported pre-bronchodilator and post-bronchodilator lung function, we used the latter.

Age of participants

The mean age of participants ranged from 40 to 71 years. Most studies had an upper age limit for participants.

Gender of participants

All but three of the studies reported the proportion of males included in the study. This ranged from 44% to 93%. In another study, "almost all" of the participants were reported as male.

Smokers

All but five studies reported the percentage of current smokers or ex-smokers, which ranged from 55% to 100%.

Mucolytics and dose

In 21 studies, the mucolytic used was N-acetylcysteine (NAC). Other treatments studied included carbocysteine (N = 3), ambroxol (N = 3), erdosteine (N = 2), sobrerol (N = 1), carbocysteine-sobrerol (N = 1), carbocysteine-lysine (n = 1), letosteine (N = 1), cithiolone (N = 1), iodinated glycerol (N = 1), N-isobutyrylcysteine (NIC) (N = 1), myrtol (N = 1), and cineole and lysozyme (N = 1).

Of the 21 studies of NAC, three used a total dose of 400 mg/day (Babolini 1980; Boman 1983; Borgia 1981); 11 used a total dose of 600 mg/day (Bachh 2007; Decramer 2005; Grassi 1976; Jackson 1984; McGavin 1985; Meister 1986; Nowak 1999; Parr 1987; Pela 1999; Rasmussen 1988; Schermer 2009); five used 1200 mg/day (Hansen 1994; Roy 2014; Tse 2013; Xu 2014; Zheng 2014); one used 1800 mg/day (De Backer 2013;); and one used 3600 mg/day (Johnson 2016).

Size and duration

Study size ranged from 12 participants in De Backer 2013 to 1006 participants in Zheng 2014. Duration ranged from 2 months in Petty 1990 and Johnson 2016 to 36 months in Decramer 2005 and Schermer 2009. The mean duration of treatment, weighted by study size, was 9.4 months. Over a third of participants were enrolled in studies lasting 12 months or longer.

Countries

Twelve studies were conducted only in Italy, four in the United Kingdom, four in Germany, four in China, four in several European countries, three in Scandinavia, two in India, two in the United States, and one each in The Netherlands, Belgium, and Japan.

Funding

We have extracted and presented information on study funding since the 2014 update. A majority of studies included since 2014 report pharmaceutical sponsorship, with the exception of Johnson 2016, Roy 2014, and Xu 2014.

Excluded studies

We excluded 20 studies after scrutiny of the full text. See Characteristics of excluded studies for the reasons for exclusion.

Risk of bias in included studies

Details of our risk of bias judgements are presented in Characteristics of included studies and in an overview in Figure 4.

Figure 4. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

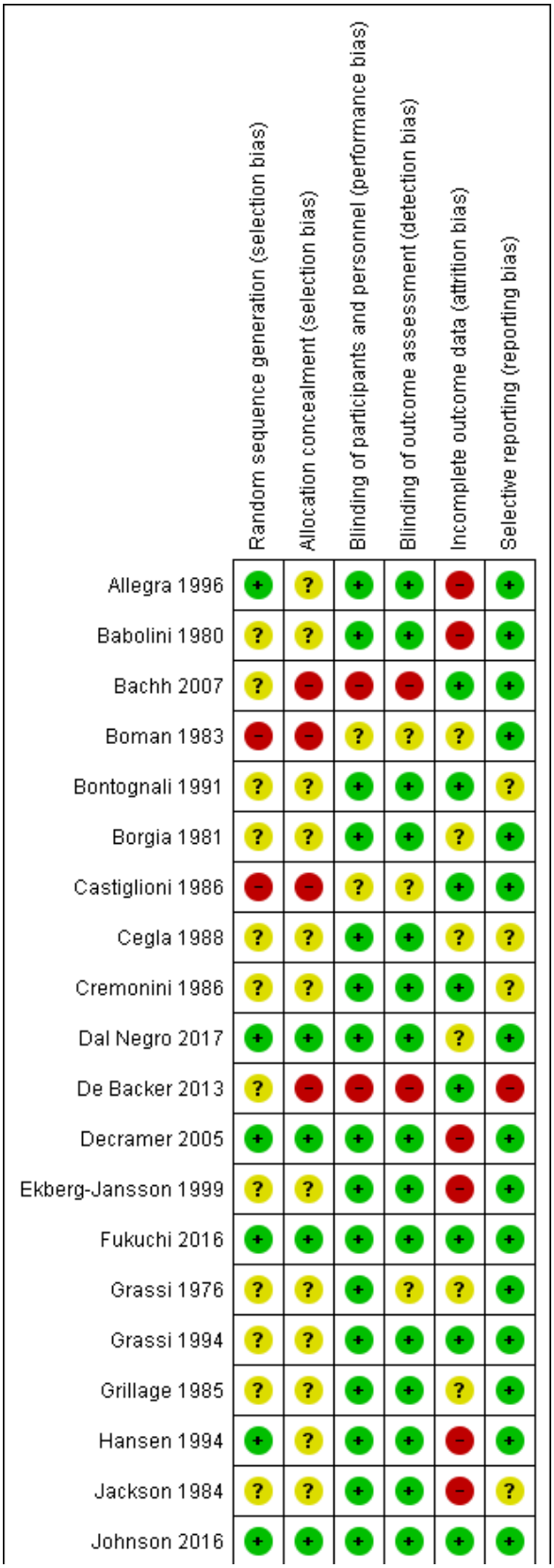
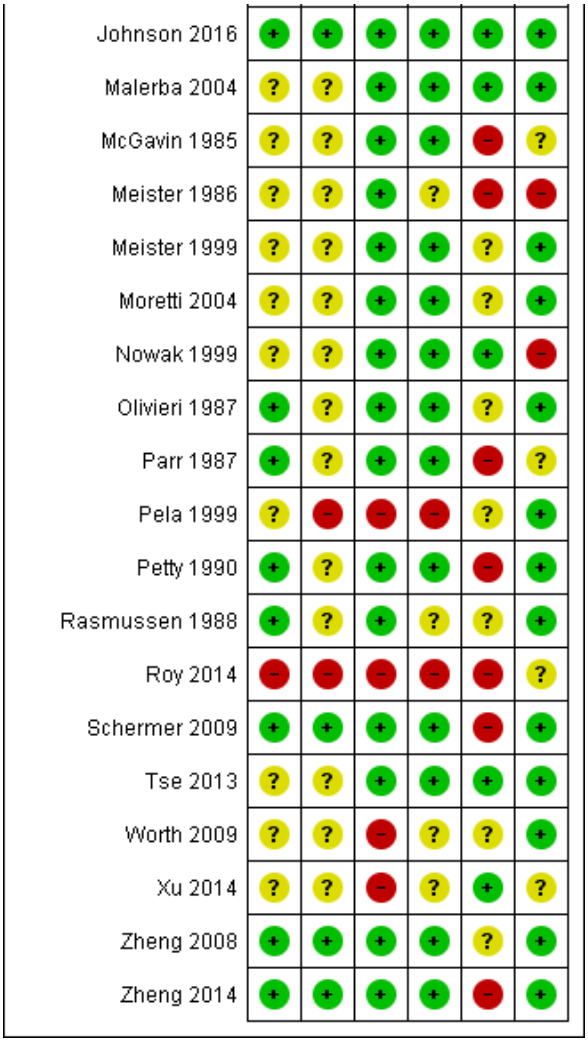


Figure 4. (Continued)



Allocation

Potential for bias in most studies was regarded as unclear, in that study authors stated that the study was randomised but did not indicate how this was achieved, where it was done, or how it was concealed. Seven studies were judged to be at low risk of bias for both random sequence generation and allocation concealment (Dal Negro 2017; Decramer 2005; Fukuchi 2016; Johnson 2016; Schermer 2009; Zheng 2008; Zheng 2014). Six studies were judged to be randomised but provided insufficient details about allocation concealment (Allegra 1996; Hansen 1994; Olivieri 1987; Parr 1987; Petty 1990; Rasmussen 1988). Six studies were judged to be at high risk of bias for one or both domains (Bachh 2007; Boman 1983; Castiglioni 1986; De Backer 2013; Pela 1999; Roy 2014).

Most studies reported baseline characteristics of treatment groups, which were well matched at baseline.

Blinding

Most studies (N = 30) reported that the placebo was identical in appearance to the active treatment and therefore were judged to be at low risk of performance bias. Six studies were regarded as high risk, which related largely to lack of blinding, although Xu 2014 provided no description of blinding, and so an open-label policy must be assumed (Bachh 2007; De Backer 2013; Pela 1999; Roy 2014; Worth 2009; Xu 2014).

Blinding of outcome assessors was less well described, but 27 studies described adequate procedures, allowing us to judge these as having low risk of bias. Four studies were at high risk of bias and seven studies reported insufficient details about detection bias to permit a judgement.

Incomplete outcome data

Reported dropout ranged from 0% in Bachh 2007, Bontognali 1991, Cremonini 1986, and Xu 2014 to 37% in the three-year BRONCUS study (Decramer 2005), and this rate was given as 43% in another three-year study conducted in a general practice setting (Schermer 2009). When the rate exceeded 20%, we considered a high-risk rating but also took into account whether numbers of dropouts were balanced between arms, and whether the reasons given for dropout were similar. We judged 13 studies to be at high risk (Allegra 1996; Babolini 1980; Decramer 2005; Ekberg-Jansson 1999; Hansen 1994 Jackson 1984; McGavin 1985; Meister 1986; Parr 1987; Petty 1990; Roy 2014; Schermer 2009; Zheng 2014). We judged 12 studies to be at low risk as dropout either was low or had been sufficiently

well described that we were confident the results of the study were unlikely to be impacted (Bachh 2007; Bontognali 1991; Castiglioni 1986; Cremonini 1986; De Backer 2013; Fukuchi 2016; Grassi 1994; Johnson 2016; Malerba 2004; Nowak 1999; Tse 2013; Xu 2014). We judged the remaining studies to be at unclear risk because dropouts were not clearly reported or were sufficiently high to raise concern, even if numbers and reasons were balanced.

In most of the older studies and in Roy 2014, analyses were performed on participants who completed the study (per protocol), whereas in more recent studies, analyses tended to be performed on an intention-to-treat basis.

Selective reporting

Three studies were graded as high risk: two because they were unpublished (Meister 1986; Nowak 1999), and one because study authors did not report all study outcomes (De Backer 2013). Most of the other studies reported sufficient details that we could make a judgement of low risk of bias.

Other potential sources of bias

None were noted.

Effects of interventions

See: **Summary of findings for the main comparison** Mucolytic compared to placebo for chronic bronchitis or chronic obstructive pulmonary disease

Mucolytic versus control

Exacerbations

Patients with no exacerbations during study period

The odds ratio (OR) for having no exacerbations over the entire study period when treatment with mucolytics was provided in double-blind trials was increased compared with placebo (Peto OR 1.69, 95% confidence interval (CI) 1.53 to 1.88; participants = 6460; studies = 26; I^2 = 62%; Figure 5; Analysis 1.1; moderate-certainty evidence). This yielded a number needed to treat for an additional beneficial outcome (NNTB) of 8 (95% CI 7 to 10; Figure 6). Inclusion of single-blind studies in the analysis had a minimal impact on the pooled effect (Peto OR 1.73, 95% CI 1.56 to 1.91; participants = 6723; studies = 28; I^2 = 62%). We also conducted a sensitivity analysis including only the studies judged to be at low risk of selection bias; this substantially reduced the number of studies in the meta-analysis, and the effect was attenuated (Peto OR 1.15, 95% CI 0.96 to 1.37; participants = 2353; studies = 5; I^2 = 40%). However, removing the eight studies included in this analysis judged to be at high risk of attrition bias had little impact on the pooled effect estimate (Peto OR 1.84, 95% CI 1.62 to 2.09; participants = 4141; studies = 20; I^2 = 50%).

Figure 5. Forest plot of comparison: 1 Mucolytic versus placebo, outcome: 1.1 Participants with no exacerbations in study period.

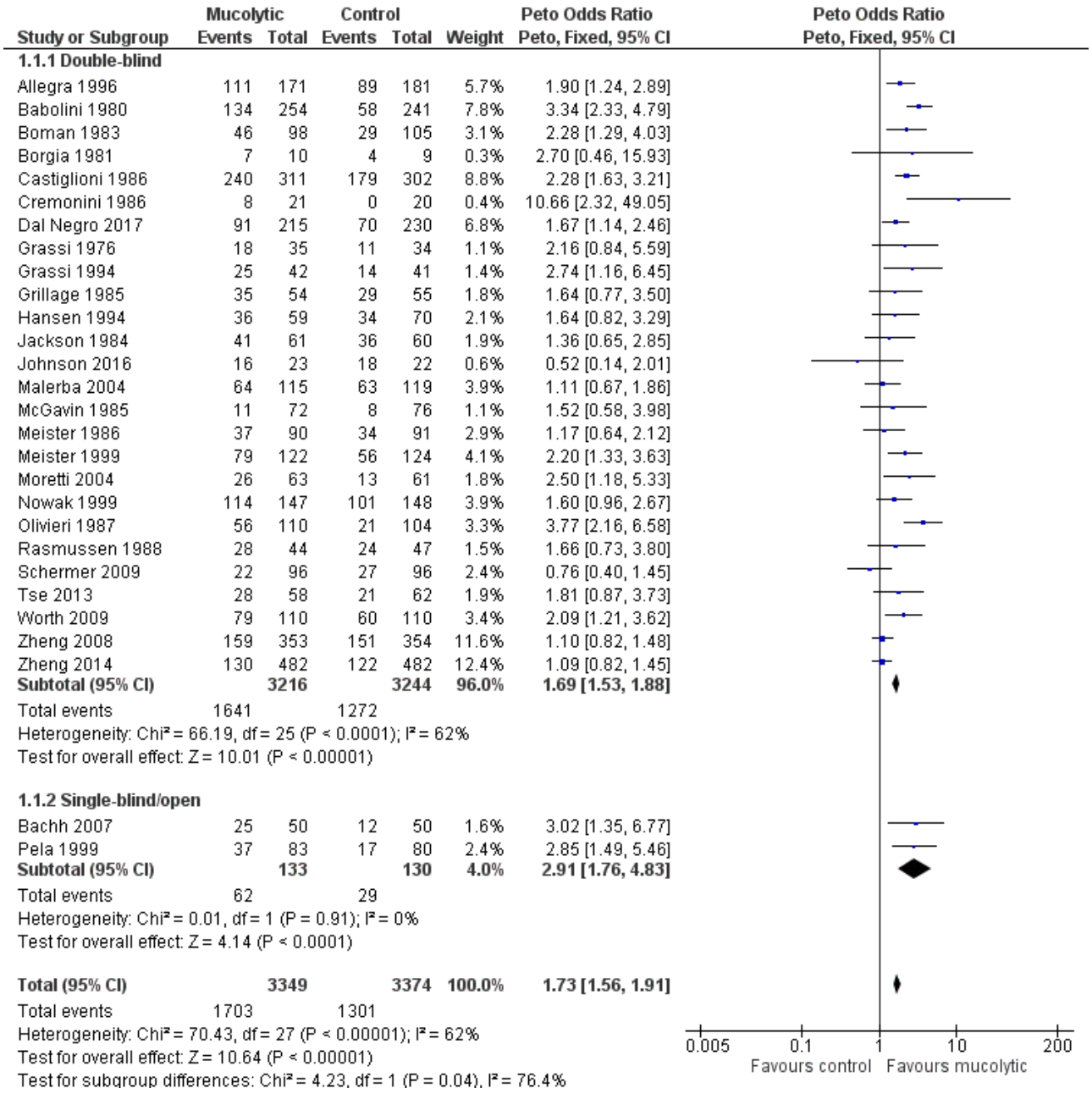
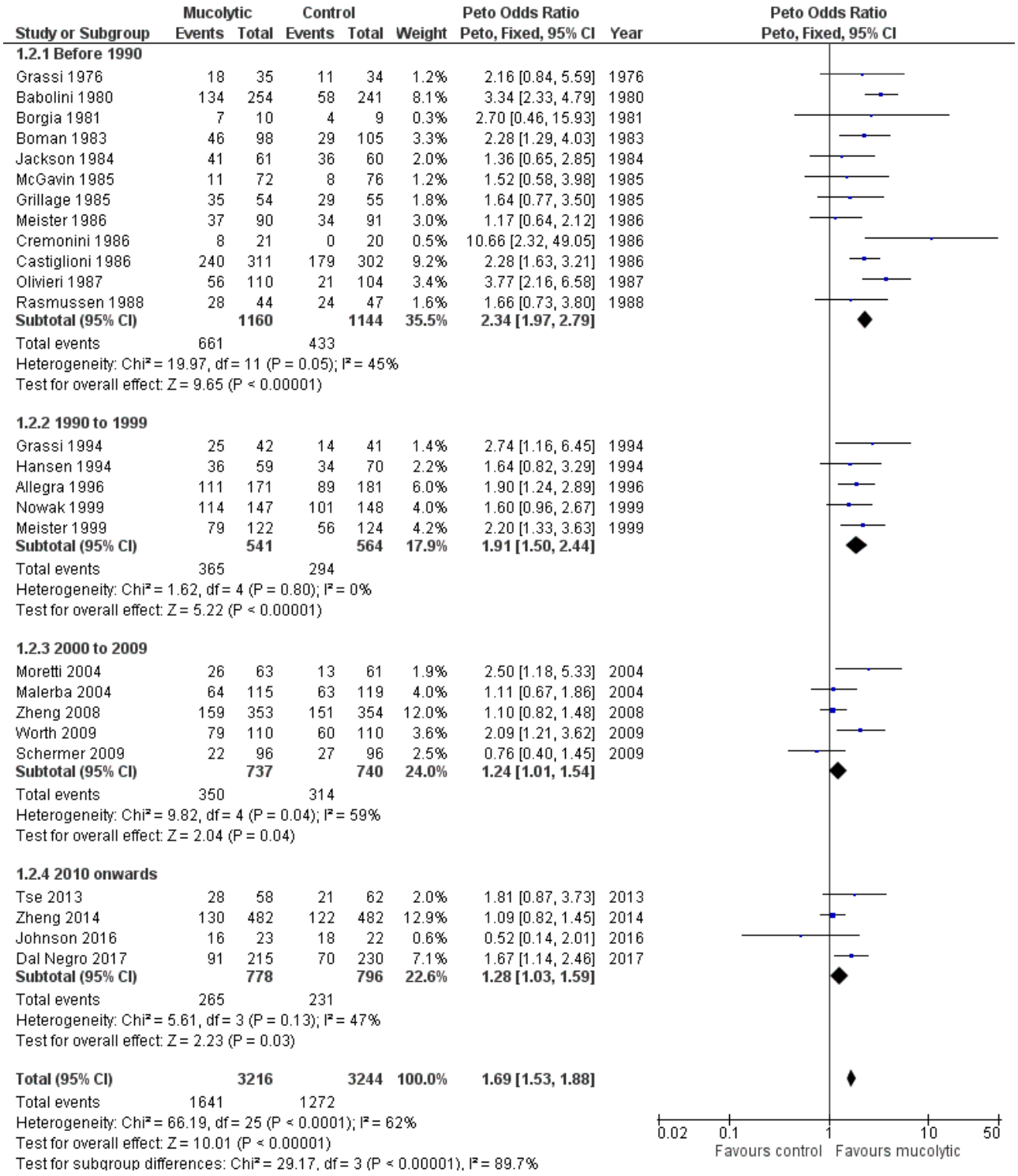


Figure 6. In the control group, 39 of 100 people were free from exacerbations over 9 months (represented by green faces) compared with 52 (95% CI 49 to 55) of 100 for the mucolytic group (represented by green plus yellow faces).

As heterogeneity in this result is high (I^2 = 62%), we carried out a post hoc subgroup analysis showing results of double-blind trials ordered by year of publication and subgrouped by decade of publication (Analysis 1.2; Figure 7). This revealed a tendency for more recent studies to provide more conservative results: studies published before 1990 (Peto OR 2.34, 95% CI 1.97 to 2.79) and between 1990 and 1999 (Peto OR 1.91, 95% CI 1.50 to 2.44) have a greater effect size than those published between 2000 and 2009 (Peto OR 1.24, 95% CI 1.01 to 1.54) or since 2010 (Peto OR 1.28, 95% CI 1.03 to 1.59). It is also notable that of the six studies with adequate allocation concealment (Dal Negro 2017; Decramer 2005; Johnson 2016; Schermer 2009; Zheng 2008; Zheng 2014), only Dal Negro 2017 reported a notable benefit of treatment in preventing exacerbations.

Figure 7. Forest plot of comparison: 1 Mucolytic versus placebo, outcome: 1.2 Participants with no exacerbation by decade; double-blind trials only.



We carried out a separate analysis of studies conducted during winter months only and observed a larger effect size when compared to all studies (Peto OR 2.20, 95% CI 1.93 to 2.51; participants = 4007; studies = 21; I^2 = 19%; Analysis 1.3). When subgrouped by dose or type of mucolytic, we did not observe a consistent effect (I^2 62%, Analysis 1.4). Overall we observed significant benefits over placebo for lower doses of NAC and carbocysteine,. The "other" mucolytic category also showed benefit compared to placebo; this category included studies of ambroxol (N = 2); erdosteine (N = 1); letosteine (N = 1); sobrerol (N = 1); myrtol (N = 1); and cineole (N = 1).

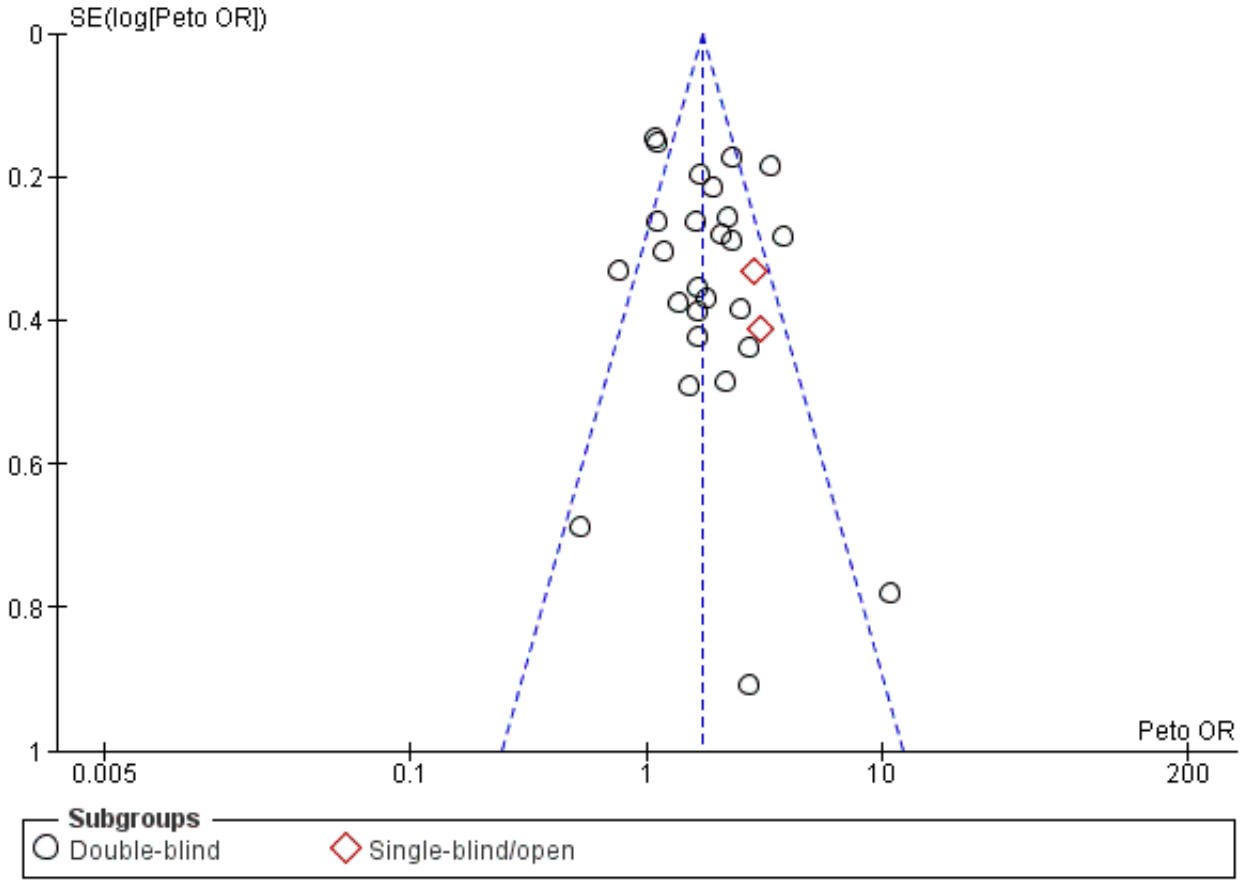
Studies with participants with on average better lung function at baseline found greater benefit from mucolytics when compared to those with on average poorer lung function (> 50% predicted vs ≤ 50% predicted; test for subgroup differences: Chi^2 = 4.14, df = 1 (P = 0.04; I^2 = 75.9%; Analysis 1.5). However, this result should be interpreted with caution as the poorer lung function subgroup contained only four studies.

Studies of greater duration on average had a lesser effect than those of shorter duration; the OR for studies ≥ 12 months was 1.16 (95% 0.98 to 1.37) compared to 2.14 (95% CI 1.62 to 2.82) and 2.20 (95% CI 1.91 to 2.54) for up to three months and three to 12 months, respectively (test for subgroup differences: Chi^2 = 35.72, df = 2 (P < 0.00001; Analysis 1.6).

We also observed a larger effect among studies conducted in Italy compared to those not conducted in Italy (test for subgroup differences: Chi^2 = 25.94, df = 1 (P < 0.00001; Analysis 1.7). This analysis was carried out as it has been noted in the past that some of the earlier trials of mucolytics in Italy were reporting greater effects than trials conducted elsewhere, We also noted a larger effect in those studies in which history of an exacerbation was not a requirement for study entry compared to those where it was (test for subgroup differences: Chi^2 = 12.51, df = 1 (P = 0.0004; Analysis 1.8).

A funnel plot for this outcome gave no clear indication of publication bias (Figure 8).

Figure 8. Funnel plot of comparison: 1 Mucolytic versus placebo, outcome: 1.1 Participants with no exacerbations in study period.



Exacerbations in patients by use of concomitant inhaled corticosteroids (ICS)

Subgrouping studies for this outcome according to whether ICS were or were not allowed (or unclear) did not suggest that this was an important effect modifier, and the test for subgroup differences was negative (test for subgroup differences: Chi^2 = 1.64, df = 2; (P = 0.44; Analysis 1.9).

Time to first exacerbation

Sufficient data with which to perform a meta-analysis are not yet available for this clinically relevant outcome. Post hoc analysis of the EQUALIFE study revealed that participants given erdosteine had a significantly longer time until their first exacerbation compared with those given placebo, with a hazard ratio of 0.639 (95% CI 0.416 to 0.981) (Ballabio 2008). Longer time to first exacerbation was also reported by Nowak 1999. In that study, participants with COPD treated with NAC had a mean of 139 days (SD 68) to first exacerbation versus 108 (SD 79) days for those given placebo (P < 0.05). More recently, Zheng 2014, Dal Negro 2017, and Fukuchi 2016 reported time to first exacerbation. Zheng 2014 reported no differences between time to first exacerbation in NAC- or placebo-treated groups, but time to second and third exacerbations was

shorter in the placebo group. Dal Negro 2017 reported increased time to first exacerbation in the erdosteine group compared to the placebo group, but this did not reach statistical significance (Kaplan–Meier plot of probability, P = 0.07). Fukuchi 2016 reported the median time to first exacerbation as 179 days in the lysozyme group and 210 days in the placebo group (hazard ratio 1.06; P = 0.626).

Number of exacerbations per patient per month

We calculated and meta-analysed the number of exacerbations per patient per month as a primary outcome in previous versions of this review. For the 2019 update, we decided not to update these analyses due to concerns about high levels of heterogeneity, the need to impute much of the data, and the likely skew of this measure. Instead, we present the data in a table (Analysis 1.10). The mean difference in number of exacerbations per patient per month favoured the mucolytic intervention in most studies, but this finding should be interpreted with caution in light of the caveats already mentioned.

Number of days of disability per participant per month ('sick days')

We were able to meta-analyse data from nine studies, showing a significant reduction of 0.43 days of disability per participant per month with mucolytic therapy (95% CI -0.56 to -0.30; 9 studies, 2259 participants; Analysis 1.11; moderate-certainty evidence) compared with placebo. This finding was associated with a high level of heterogeneity (I^2 = 61%).

The following studies reported information that we were unable to meta-analyse. Cegla 1988 reported total days off sick per group over the two years and noted that this did not differ significantly between the two treatments (1071 days in the ambroxol group and 979 in the placebo group over two years; participants = 180). Nowak 1999 reported the cumulative exacerbation days per group as 462 days in the NAC group and 776 days in the placebo group over eight months (participants = 295). Petty 1990 reported the mean duration in days of exacerbations between week 4 and week 8 of the trial. The mean duration in the iodinated glycerol group was 6.3 compared to 10.2 in the placebo group; the P value for the difference was reported as 0.029 (participants = 376). Moretti 2004 did not report total 'sick days'; however, investigators did report the numbers of individuals losing workdays: seven in the erdosteine group and 10 in the placebo group, for a mean number of days lost per person of 0.8 and 1.1, respectively.

In the three studies that reported it, a mean reduction of 0.53 days on antibiotics per participant per month was observed (95% CI -0.76 to -0.31; 3 studies; 714 participants; Analysis 1.12). These were older studies that included participants with chronic bronchitis. In the study of Meister 1999, 6/31 (52%) participants in the myrtol group with exacerbations needed antibiotics, compared with 30/49 (61%) in the placebo group. Courses of antibiotics were longer in the placebo group. The percentage of participants who needed antibiotics for longer than seven days was 37% in the myrtol group and 77% in the placebo group. Malerba 2004 reported no differences between ambroxol and placebo in terms of duration of courses of antibiotic treatment, working days lost, or number of days of hospitalisation (no data given). Moretti 2007 used post hoc analyses to report that compared with placebo, erdosteine use was associated with relatively fewer antibiotic courses (32%) and shorter durations of treatment (15%). The mean number of antibiotic courses per participant treated with erdosteine was also lower than for those given placebo (0.5 (SD 0.7) vs 0.7 (SD 0.7); P = 0.045).

Lung function

FEV_1

Fourteen studies reported FEV_1 in L at the end of the study. The pooled effect favours mucolytics over placebo, but the effect size is small (mean difference (MD) 0.04 L, 95% CI 0.01 to 0.07; participants = 3310; Analysis 1.13; moderate-certainty evidence). We observed substantial heterogeneity in this outcome (I^2 = 70%), and so results should be interpreted with caution. Furthermore, this analysis includes data from the Moretti 2004 study, which reported a significant difference (> 300 mL) between mucolytic and placebo groups at the end of the study; however the mucolytic group had higher baseline lung function, and the net change was therefore closer to 200 mL. If this study is removed from the analysis, a significant difference between groups is no longer observed and heterogeneity is removed.

Nowak 1999 reported FEV_1 change from baseline in L but without variance, and so we were unable to include the results in the meta-analysis. Trialists reported 0.225 L improvement in the NAC group (n = 33), compared to 0.062 L in the placebo group (n = 47).

Of note, two three-year studies are included in this analysis. The BRONCUS study of Decramer 2005 found no differences between NAC-treated and placebo-treated groups over three years in terms of decline in FEV_1, FVC, or diffusing capacity of the lung for carbon monoxide (DLCO). FEV_1 declined by 54 mL and 47 mL, respectively, in the two groups. Study authors reported possible benefit of NAC for functional residual capacity (FRC), with a greater reduction in this measure. The difference was -0.374 L (SD 1.03; P < 0.01) for NAC-treated participants, whereas for those treated with placebo, a decrease of only 0.008 L was reported. The other three-year study found no differences between groups in lung function at the end of the study (Schermer 2009). In the NAC-treated group, FEV_1 declined by 64 mL, and in the placebo group, by 60 mL. The decline in FVC was 79 mL and 65 mL, respectively.

In the HIACE study of Tse 2013, a significantly higher mean FEV_1 was reported for the NAC group at the end of the study, but this reflected differences at baseline, with no significant differences in the amount of change reported between groups. On the other hand, researchers reported significantly greater changes in the NAC group than in the placebo group for two measures of small airways function: forced expiratory flow at 25% to 50% (FEF_{25-50}) (P = 0.037) and forced oscillation technique (FOT) (P = 0.04), as well as for airways resistance (P = 0.01).

Percent predicted FEV_1

This outcome was reported by only four studies. Although the pooled effect favours mucolytics, this is driven by one study: Xu 2014, which was not blinded (MD 4.79, 95% CI 1.97 to 7.62; participants = 414; Analysis 1.14), and again, we detected substantial heterogeneity (I^2 = 89%).

Peak expiratory flow rate

Peak expiratory flow rate was reported by one study only (Grillage 1985). The result favours mucolytics but is very uncertain (MD 19.00, 95% CI -22.70 to 60.70; participants = 109; Analysis 1.15).

Forced vital capacity

Twelve studies reported this outcome, and the pooled effect revealed benefit of 50 mL of mucolytics over placebo (MD 0.05, 95% CI -0.00 to 0.10; participants = 3127; I^2 = 0%; Analysis 1.16), but the confidence interval includes no difference between groups.

In summary, it is likely that if mucolytics affect disease progression in chronic bronchitis or COPD, changes are very small and are confined to as-yet small and undefined subgroups.

Adverse effects

The meta-analysis of total numbers of adverse effects favours mucolytic treatment, but with some heterogeneity (OR 0.84, 95% CI 0.74 to 0.94; I^2 = 46% participants = 7264; studies = 24; Analysis 1.17; moderate-certainty evidence). If a random-effects model is used, this finding is less precise and the confidence interval includes no difference (OR 0.83, 95% CI 0.69 to 1.00).

Moreover, this analysis does not include data from several large studies. Parr 1987 reported 1263 events in 258 participants in the mucolytics group (mean 4.9 per participant) and 1202 events in 268 participants in the placebo group (mean 4.5 per participant). Decramer 2005 reported 1428 events in 256 participants in the mucolytics group (mean 5.58 per participant) and 1381 events among 267 participants in the placebo group (mean 5.17 per participant). None were thought to be drug-related. Similar numbers in each group were admitted to hospital (55 and 69, respectively). Another study described 54 events in 59 participants in the mucolytic group and 66 events in 57 participants in the placebo group (Rasmussen 1988). Meister 1999 reported 201 adverse effects in 122 participants in the mucolytic group (1.65 per participant) and 170 adverse effects in 124 participants in the placebo group (1.37 per participant). These studies could not be included in the meta-analysis because event rates exceeded numbers included in the treatment groups. Malerba 2004 also reported no greater risk of events and no greater severity of events with mucolytic treatment compared with placebo.

Hospitalisation

Comparative data were provided by five studies (Decramer 2005; Johnson 2016; Moretti 2004; Tse 2013; Zheng 2014). The Peto OR for hospitalisation with mucolytic treatment compared with placebo was 0.68 (95% CI 0.52 to 0.89; participants = 1833; Analysis 1.18; moderate-certainty evidence); however, moderate heterogeneity in this result was observed (I^2 = 43%), and benefit was seen in only the two smaller studies (Moretti 2004; Tse 2013). Malerba 2004 reported no significant differences in hospitalisation rates but did not provide data. Bachh 2007 reported a significant reduction ($P < 0.05$) in hospitalisation when four months of NAC treatment was provided, with 55 hospitalisations reported for 50 participants in the control group but for only 37 of 50 in the treated group. As presented, these data cannot be included in the meta-analysis because the number of events exceeds the number of participants in the control group. If a conservative estimate of hospitalisations in the control group is made by entering them as 50 (not 55), the beneficial effect of mucolytics for hospitalisation is greater (OR 0.62, 95% CI 0.48 to 0.80) but heterogeneity is increased (I^2 = 76%). Mucolytics may be associated with a small decrease in hospitalisations.

Days in hospital were reported by Moretti 2004. In this study, participants taking erdosteine spent 70 days in hospital, compared with 163 days for the placebo group (P = 0.04). This represented a mean of 1.1 days per treated participant compared with 2.7 days per control participant.

Mortality

Eleven studies reported on numbers of deaths in mucolytic-treated and placebo groups, revealing no significant differences, but the confidence interval is wide (Peto OR 0.98, 95% CI 0.51 to 1.87; participants = 3527; Analysis 1.19; moderate-certainty evidence). As no deaths were reported in either group in Johnson 2016, Xu 2014, or Zheng 2008, this information could not be incorporated into the meta-analysis.

Health-related quality of life

Although many studies reported participant and/or physician global assessments of well-being, only ten used validated tools to evaluate health-related quality of life (HRQoL) among participants with COPD. In nine studies, investigators used the St George's Respiratory Questionnaire (SGRQ; Jones 1992) (Dal Negro 2017; De Backer 2013; Decramer 2005; Johnson 2016; Moretti 2004; Tse 2013; Worth 2009; Zheng 2008; Zheng 2014). Schermer 2009 used the Chronic Respiratory Questionnaire (CRQ; Guyatt 1987). In Johnson 2016, trialists reported the Short Form-36 (SF-36) as well as SGRQ, and in Fukuchi 2016, trialists reported the COPD Assessment Test (CAT).

The SGRQ total score is derived from scores on three subscales - symptoms, activities, and impacts - to yield a score out of 100 (Jones 1992). A well person has respiratory disease scores around 7 (Jones 1992). Lower scores indicate better quality of life.

We were able to combine total scores on the SGRQ for seven studies at the end of the treatment period. Although the pooled result favoured mucolytics over placebo, the confidence interval included no difference (MD -1.37, 95% CI -2.85 to 0.11; studies = 7, participants = 2721; Analysis 1.20; moderate-certainty evidence). Considerable heterogeneity among studies was apparent (I^2 = 64%). This effect does not meet the minimum clinically important difference of -4 units on the SGRQ (Jones 2005). However it is not possible to assess the impact of mucolytics at a population level without performing a responder analysis, which we have been unable to do.

The analysis includes data from the three-year Decramer 2005 study of 600 mg NAC daily, in which participants were evaluated with the SGRQ, although for technical reasons only about 80% of participants completed the questionnaire. During the first year of the study, participants in both treatment and placebo groups showed significantly improved scores on both scales, with no significant differences between groups (-3.76 units on NAC and -4.95 units on placebo; difference between groups 1.18; P = 0.358, as reported in the text of the paper). In the second year, this improvement tailed off again, with no differences noted between treatment groups. More participants given placebo withdrew from the trial, and dropouts had a worse SGRQ score than those who remained in the study. We have used data provided by study authors as obtained from the mixed-effects model used in this study. In a one-year study of a higher dose of NAC (600 mg twice daily; Tse 2013), no significant difference was observed between groups for SGRQ.

In Zheng 2008, baseline SGRQ scores were well matched among groups. After 12 months of treatment, changes in SGRQ total scores from baseline amounted to -4.06 units in the carbocysteine group and -0.05 in the placebo group, but these values did not represent a statistically significant difference between groups (P = 0.13). A very large difference in SGRQ symptom domain results between the carbocysteine group (-11.34 units) and the placebo group (-3.54 units; P = 0.004) remains unexplained. Results from the single measurement obtained at one year in this study contrast with multiple measurements taken in Decramer 2005, by which no significant differences in symptom scores between NAC and placebo were found over time.

In Worth 2009, the mean score change at six months from baseline was -4.3 in the placebo group and -9.9 in the cineole group (P = 0.06). However, we judged this study to be at high risk of selection bias.

In the recent one-year Dal Negro 2017 study of erdosteine, trialists reported improvements in SGRQ in both intervention and control groups but no differences between groups. Similarly, in the eight-month Moretti 2004 study of erdosteine, participants completed both SF-36 and the SGRQ. The erdosteine-treated group showed significant improvement in all domains of the SGRQ, as well as in total score, and no differences between treated and placebo groups were reported. Data from Moretti 2004 were not suitable for inclusion in Analysis 1.20.

In the three-year study of NAC versus placebo (Schermer 2009), the CRQ was used. Groups were well matched at baseline, with evident improvement in both groups, particularly over the first year, but this never exceeded the 0.5 unit threshold regarded as clinically significant (Guyatt 1987). At the end of the study, no significant differences in CRQ total scores were reported between groups (P = 0.306).

In Fukuchi 2016, CAT scores were reported. Trialists reported that quality of life in both the lysozyme group and the placebo group improved according to this measure; improvement was greater in the lysozyme group at all time points, and the difference was significant at 24 weeks but did not remain so at 52 weeks (MD -0.90, 95% CI -2.22 to 0.42; participants = 340; studies = 1, Analysis 1.21).

Thus, considerable variation can be seen in evidence related to HRQoL, and we are not able to assess whether mucolytics had a clinically important effect on this outcome. Furthermore, and in keeping with the exacerbation outcome, more recent studies have tended to provide more conservative estimates of the impact of mucolytics on quality of life.

Systemic thiol donor versus control

One study investigated a systemic thiol donor, N-isobutyrylcysteine (NIC), versus control (Ekberg-Jansson 1999). This trial randomised more than 600 participants with chronic bronchitis. There was no clear difference between groups for the number of participants who remained exacerbation-free (Peto OR 1.01, 95% CI 0.74 to 1.39; participants = 628; Analysis 2.1), the number of exacerbations per participant per month (MD 0.01; 95% CI -0.02 to 0.04), or days of disability per participant per month (MD -0.18, 95% CI -0.82 to 0.46; participants = 628; Analysis 2.3). Participants in the intervention group experienced more adverse events, but the confidence interval included no difference (Peto OR 1.39, 95% CI 0.98 to 1.95; participants = 628; Analysis 2.4).

DISCUSSION

Summary of main results

The previous update of this review was performed in 2015 (Poole 2015). Since that time, a further four studies that were eligible for inclusion have been conducted (Dal Negro 2017; Fukuchi 2016; Johnson 2016; Xu 2014). The present update strengthens findings from our previous reviews indicating that participants given a mucolytic agent for an average of nine months are more likely to be exacerbation-free during that time (Peto odds ratio (OR) 1.73, 95% confidence interval (CI) 1.56 to 1.91). For one participant to be exacerbation-free, eight (95% CI 7 to 10) had to be treated for at least nine months. Mucolytics may be associated with a reduction of approximately a half-day of disability per participant per month, but the result is heterogeneous (mean difference (MD) -0.43, 95% CI -0.56 to -0.30; I^2 = 61%). Three studies reported days on antibiotics per participant per month, and the pooled result indicated benefit of mucolytics (MD -0.53, 95% CI -0.76 to -0.31).

Mucolytics may be associated with a decrease in hospitalisations, although this finding is based on data from only five studies (Peto OR 0.68, 95% CI 0.52 to 0.89). With the addition of newer studies, certainty that mucolytics do not have a substantial impact on lung function decline or mortality is increasing. Mucolytics may be associated with a reduction in all adverse events, but the effect estimate includes the possibility of no difference between groups (OR 0.83, 95% CI 0.69 to 1.00). The impact on quality of life as measured by the total St. George's Respiratory Questionnaire (SGRQ) score is smaller than the minimal clinically important difference (MCID) of 4 units and also includes the possibility of no differences between groups (MD -1.37, 95% CI -2.85 to 0.11). Furthermore, we cannot be certain about the population effect, as we were unable to carry out a responder analysis.

For many outcomes - primary and secondary - significant heterogeneity has been noted among studies; therefore the results do need to be interpreted with particular caution. The only outcomes for which heterogeneity among trials was not significant were days on antibiotics, forced vital capacity (FVC), and death during the study period. To explore causes of heterogeneity for the primary outcome of exacerbations, we performed subgroup analyses according to study date, baseline forced expiratory volume in one second (FEV_1) (as % predicted), type of mucolytic, dose of mucolytic, duration of therapy, whether participants were included because they had a history of exacerbations, whether concomitant inhaled steroids were used, and the country in which the study was conducted. Heterogeneity was generally less among trials with winter treatment only and those using the same dose of N-acetylcysteine (NAC).

The tendency for participants given mucolytics to be more likely to be exacerbation-free was seen in all studies except Schermer 2009 and Johnson 2016. Schermer 2009 was the first study that found an increased number of exacerbations in the mucolytic-treated group compared with the placebo-treated group; however, this difference was not statistically significant. The exacerbation rate was generally low in this study, and data were skewed by two participants in the NAC-treated group who had very frequent exacerbations. Additionally, this study reported a high dropout rate (43%). Johnson 2016 also reported increased exacerbations in the mucolytic group, but the result was very imprecise and was

reported in the context of a study stopped at eight weeks due to safety concerns after only 51 participants were recruited.

However, when we performed a post hoc investigation comparing more recent study results versus those from previous decades, we found a clear reduction in the effects of treatment in more recent studies (see Figure 7; I^2 = 89.7% between subgroups). Although all studies included in this analysis were placebo-controlled, and most were double-blind, the older studies were more difficult to judge in terms of bias (see Figure 4), and this may have led to an overestimation of treatment effect. Therefore we have a reduced level of confidence in the overall treatment effect estimate. On the other hand, internal consistency is evident in the findings, in that the effect on exacerbations rate is accompanied by a reduction in hospitalisations and a reduction in both days of disability and days on antibiotics.

Theoretical reasons have been proposed to explain why mucolytics may modify disease in ways other than by reducing exacerbations (i.e. through antioxidant and thiol donor effects). More recent studies have sought to explore whether the decline in FEV_1 over time is changed by mucolytics. NAC has been used at higher doses or for longer durations without providing additional benefits, although this may be due to insufficient power to detect a difference. The reduction in exacerbation rates seen with NAC was virtually identical to that observed with other mucolytics examined as a group. The mechanisms responsible for the benefits of mucolytic treatment for exacerbation rates and days of disability cannot be identified by this review. However, lack of effect of N-isobutyrylcysteine (NIC) (a thiol donor with antioxidant properties) on exacerbation rates or days sick raises the possibility that the actions of NAC as a thiol donor are less important in the reduction of exacerbations.

We found no evidence to suggest that mucolytics are unsafe, and findings indicate that they do not adversely affect quality of life, even though medicines need to be taken at least once a day.

Overall completeness and applicability of evidence

This review has now been updated substantively seven times. Through the process of iterative searches, we are confident that we have identified almost all the major studies with mucolytics as the intervention.

Over time, with a steady increase in the numbers of studies published, even though a significant treatment effect of mucolytics on exacerbations has always been observed, the size of this effect has decreased from that described in the original report. This trend may be observed in Figure 7, where studies have been separated by decades of publication.

We have considered below two factors that may be contributing to this observation.

Improved study design, execution, and reporting over the years

Confidence intervals are narrower, and consequently greater weight is afforded to more recent studies. The forest plot in Figure 7 has been arranged in subgroups by date and shows this trend. Part of the explanation is that more recent studies, on average, have been larger than earlier ones. Another consideration is that publication bias may have influenced reporting of results of earlier trials. This is suggested by asymmetrical funnel plots in Analysis 1.11 and Analysis 1.13 (Figure 1 and Figure 2).

Furthermore, tighter definitions of chronic obstructive pulmonary disease (COPD) have been used in later studies, which have generally included patients with, at most, moderate disease. To be included in earlier studies, patients needed only to have symptoms of chronic bronchitis, which is a clinical diagnosis. Furthermore, fewer dropouts in the intervention groups of longer studies might dilute any treatment effect, as those remaining in the study have a longer period over which to have an exacerbation recorded. Finally, as was mentioned previously, older studies may be at greater risk of selection bias, which may have inflated estimates of the treatment effect.

Improved COPD care

Comprehensive management of COPD now includes support for smoking cessation, vaccination, pulmonary rehabilitation, and use of inhaled corticosteroids (ICS), long-acting beta-agonists (LABAs), and anticholinergic agents (GOLD 2019), each of which may impact exacerbation frequency or severity.

Inhaled corticosteroids have been available for asthma since the late 1970s, but it is unlikely that they were used by participants with chronic bronchitis in trials before 1990. In most of the other studies, ICS treatment was allowed. In the present review, we divided the studies into whether cotreatment with ICS was allowed, not allowed, or unclear (Analysis 1.9). There was no significant subgroup difference (P = 0.44), suggesting that the effect of mucolytics is not affected by ICS use. The nature of reporting of the studies did not allow us to stratify by use of measures mentioned previously that may reduce exacerbations.

The trend in the likelihood that participants in control groups would be exacerbation-free is 38% in pre-1990 studies, 52% between 1990 and 2000, 42% from 2000 to 2009, and 29% from 2010 onwards (derived from Analysis 1.2). These findings suggest that up to 40% of study participants with COPD will have an exacerbation. One interpretation is that more recent studies show a trend toward improvement in overall care, but this needs follow-up.

Quality of the evidence

We graded all pooled outcomes as moderate, indicating that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (Summary of findings for the main comparison). Our confidence in the pooled estimates was reduced by several considerations. Most outcomes were both clinically diverse and statistically heterogeneous.. Trials used a variety of types and doses of mucolytic, were conducted over two months to three years, and recruited populations with different baseline severity of COPD. Many were conducted in the 1980s and 1990s, at which time standard definitions and standard treatment for COPD differed from today. Subgroup analysis applied to our primary outcome of exacerbations explained some, but not all, the statistical heterogeneity. Therefore all outcomes, with the exception of mortality, were downgraded for inconsistency.

Although we had concerns about the conduct methods used for some of the included trials, including uncertainty about methods of allocation concealment and blinding, we did not downgrade any outcome for risk of bias, as the trials about which we had greatest concern were generally of low weight in the meta-analyses. We also

judged 13 studies to be at high risk of attrition bias due to high or unbalanced dropout. To explore this further, we conducted a post hoc sensitivity analysis on our primary outcome (participants with no exacerbations during follow-up). Removal of studies considered to be at high risk of attrition bias had a minimal impact on the pooled effect estimate.

Funnel plots for days of disability and FEV_1 outcomes (Figure 1 and Figure 2) suggest a possible small-study effect (i.e. missing small negative trials). Removing the small positive trials from the analyses had minimal impact on the pooled result; therefore we did not downgrade for this reason. Furthermore, a funnel plot for the primary outcome participants with no exacerbation appeared symmetrical, giving no indication of publication bias (Figure 8).

We considered a downgrade for imprecision for health-related quality of life, but although the confidence interval includes no difference, both ends lie within the MCID for SGRQ, and thus we are reasonably confident that mucolytics do not have a substantial impact on quality of life. However, we did downgrade mortality for imprecision, as the confidence interval of the pooled effect estimate includes both important harm and benefit of the intervention.

Finally, although we considered indirectness on the basis of the age of some of the included studies, we did not judge our concerns to be sufficiently serious to warrant a downgrade.

Potential biases in the review process

The subgroup analysis by decade of publication is post hoc for updates from 2012 onward and should be interpreted with caution. In a few analyses, we have imputed standard deviations. When this has been done, it has been done conservatively and in accordance with accepted practices. This could have narrowed the confidence intervals for individual studies, thus increasing heterogeneity. Furthermore, the approach that we used may tend to overestimate the number of exacerbations per year in both groups, as more occur during the winter months, when many of these studies were performed.

Despite the use of a consistent approach, slight rounding errors may have been introduced by the calculation of exacerbation rates per participant per month from study data to fit into earlier versions of RevMan that allowed only two decimal points. Furthermore, we decided to remove the meta-analysis for this outcome for the 2019 update, as we made a post hoc decision that this analysis is less robust than the dichotomous exacerbation outcome. Reasons include likely skew, high heterogeneity, and reliance on calculated/imputed data for this analysis.

Agreements and disagreements with other studies or reviews

In addition to this review, we have identified five other systematic reviews of the effects of NAC in chronic bronchitis/COPD. Our results are consistent with these findings. The largest of these reviews included 13 randomised controlled trials (RCTs) (Cazzola 2015). This meta-analysis reported that patients treated with NAC had significantly and consistently fewer exacerbations of chronic bronchitis or COPD (risk ratio (RR) 0.75, 95% CI 0.66 to 0.84).

The second review demonstrated that individuals treated with NAC were more likely to remain exacerbation-free (OR 1.56, 95% CI 1.37 to 1.77), with a number needed to treat for an additional beneficial outcome (NNTB) of 6 (95% CI 5 to 9) (Stey 2000). Participants were more likely to report improvement in symptoms with NAC (OR 1.78, 95% CI 1.54 to 2.05) than with placebo. The third review analysed nine trials that had been included in both Stey 2000 and this Cochrane review, and confirmed a significant effect on exacerbations (standardised mean difference (SMD) -1.37, 95% CI -1.5 to -1.25) (Grandjean 2000). A meta-analysis published in 2017 investigating the effects of NAC on exacerbations of COPD showed that both high-dose (RR 0.90, 95% CI 0.82 to 0.996) and low-dose (RR 0.83, 95% CI 0.69 to 0.99) NAC reduced COPD exacerbations (Fowdar 2017). Therefore, the review concluded that long-term therapy may reduce risk of COPD exacerbation, which is in agreement with our findings.

The fifth review investigated the use of mucolytics and antioxidants for COPD (Li 2015; abstract only available in English). The review includes 10 RCTs and reports that mucolytics and antioxidants reduce the number of exacerbations per patient per year compared to placebo, and that high-dose NAC may be more effective than low-dose, although a test for subgroup differences was not reported in the abstract.

The analyses in this review suggest that mucolytics might, in addition, have an effect on duration and severity of exacerbations that do occur, and on the likelihood of taking antibiotics. Data from four studies suggest that mucolytics are associated with decreased hospitalisation rates. It would be helpful if future studies looked at this outcome, as this is where most costs associated with more severe disease are incurred. Few other pharmacological treatments have been shown to reduce hospitalisation: an immunomodulatory agent OM-85 BV, or Broncho-Vaxom (Collet 1997), was shown to reduce the number of hospital admissions in COPD, even though it did not affect the number of exacerbations.

Researchers performed a retrospective cost-effectiveness analysis of NAC in chronic bronchitis that was based on direct costs of NAC treatment, management of an acute exacerbation, and indirect costs of sick leave (Grandjean 2000a). Results suggest that costs of treatment and non-treatment were equal at the point of a reduction of 0.6 exacerbations per six-month period. In our review, a reduction of about 0.18 per six-month period suggested that it would not be cost-effective to treat everyone with COPD with mucolytics.

Bachh 2007 and colleagues from India estimated the cost of prophylactic NAC therapy to be INR 6000 (USD 120), whereas a short course of oral corticosteroids (OCSs) and antibiotics would cost INR 200 (USD 4). ICSs are also expensive. As the burden of COPD over coming decades is going to disproportionately affect developing nations, the relative costs of each strategy are important to determine.

Several national and international guidelines make recommendations about the use of mucolytics. In a recent North American guideline on treatments to prevent COPD exacerbations, NAC was suggested for patients with moderate or severe COPD and a history of two or more exacerbations in the previous two years (evidence grade 2B - weak recommendation; moderate-quality evidence; Criner 2015). Furthermore, carbocysteine was suggested (ungraded consensus-based statement) for patients still having exacerbations in spite of maximal therapy provided to reduce exacerbations. This is consistent with the more recent

Joint American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines for prevention of exacerbations, which gives a conditional recommendation for the use of mucolytics in patients with moderate to severe airflow obstruction and frequent exacerbations despite optimal therapy, based on low-quality evidence (Wedzicha 2017). The 2019 update of the global COPD guidelines states that NAC may have a role in the treatment of patients with recurrent exacerbations (evidence grade B - moderate-quality evidence), and that carbocysteine or NAC may reduce exacerbations in patients not taking inhaled steroids (grade B) (GOLD 2019). COPD-X guidelines give a stronger recommendation in favour of high-dose oral NAC (Yang 2018), and UK National Institute for Health and Care Excellence (NICE) guidelines suggest use in patients with chronic cough productive of sputum and continued only if there is symptomatic improvement (NICE 2018).

AUTHORS' CONCLUSIONS

Implications for practice

Mucolytics may reduce the number of exacerbations in people with chronic bronchitis or chronic obstructive pulmonary disease (COPD) by a small quantity, and do not appear to be associated with an increase in adverse events. Approximately one person in eight may avoid having an exacerbation, provided all take treatment every day for an average of nine months. Mucolytics are associated with a reduction in days of disability per month and a reduction in hospitalisations in the studies that reported this outcome. Mucolytics have not been shown to substantially slow the decline in lung function, and it is uncertain whether they improve quality of life. Results are too imprecise to be certain whether or not there is an effect on mortality. As reduction in exacerbations seems the main potential benefit, mucolytics might be considered (1) a treatment option for patients with frequent exacerbations who cannot take other therapies such as inhaled corticosteroids or long-acting bronchodilators, which have a stronger evidence base for their effectiveness; or (2) as add-on treatment once all other therapies to reduce exacerbations have been utilised.

Implications for research

Future studies might address the value of mucolytic therapy:

- in patients who have multiple exacerbations per year, or who have prolonged or severe exacerbations;
- in patients already receiving current guideline-based therapy; and
- in patients with repeated admissions to hospital with exacerbations of COPD despite maximal therapy to reduce acute exacerbations of COPD.

Studies should stratify participants by (1) the new GOLD criteria (A-D; GOLD 2019), which incorporate symptoms and exacerbations, as well as spirometry; and (2) use of concomitant medications (such as inhaled corticosteroids (ICSs), long-acting bronchodilators, or macrolide antibiotics).

Outcomes of studies should include hospitalisations (COPD and all-cause), mortality (COPD and all-cause), numbers of days sick with exacerbations, and a validated measure of quality of life. A responder analysis for quality of life would add valuable information on the population effects of treatment.

ACKNOWLEDGEMENTS

This review is dedicated to the memory of Professor Peter Black, FRACP, who died in 2010. Peter made significant and broad contributions to asthma and COPD research, including work as a reviewer and editor for the Cochrane Airways Group.

We would like to acknowledge the contributions of the following.

- Peter Black, who was the co-author of the first four versions of this review.
- Emma Dennett, Peter Gibson, Paul Jones, and Toby Lasserson of the Cochrane Airways Group for editorial support.
- Emma Jackson, Anna Bara, Karen Blackhall, and Liz Stovold of the Cochrane Airways Group for searching and retrieving full-text articles.
- Translators Ms. Sharon Kramer, Dr Silvana Campanella, Dr Ruth Black, Dr Klaus Lehnert, Ms. Daniela Screnci, and Mr. Toby Lasserson.
- Professor Marc Decramer, who provided information on SGRQ scores from Decramer 2005.
- Dr Zheng, who gave us more information on Zheng 2008 and Tatsumi 2007a, as well as the appendix to Zheng 2014. For the latter study, Dr Zheng kindly provided further data on exacerbation rate, SGRQ, and spirometry.
- Dompe Farmaceutici (Allegra 1996), which provided us with further data.
- Zambon Group for providing the Meister 1986 study and for further information on Nowak 1999.
- Douglas Pharmaceuticals and G. Pohl Boskamp for information on Meister 1999.
- Professor Roberto Dal Negro, who provided additional information on Dal Negro 2017.
- Dr Dennis Niewoehner, who provided additional information on Johnson 2016.
- Professor Inoue, who provided additional information on Fukuchi 2016.
- Other study authors and companies that took the trouble to write back, even though they could not provide further data (Dr Petty, Dr Boman, Novartis Pharmaceuticals).

Sally Spencer was the Editor for this review and commented critically on the review.

The review authors and Cochrane Airways are grateful to the following peer reviewers for their time and comments: Craig P. Hersh, Brigham and Women's Hospital; Prof. Marc Decramer, University Hospital Gasthuisberg, Leuven, Belgium; and our consumer reviewer, Andy Coles, for assessing the plain language summary.

The Background and Methods sections of this review are based on a standard template used by Cochrane Airways.

This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Airways Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS, or the Department of Health.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Allegra 1996

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre study, with 1 month run-in before randomisation. Duration 6 months. ITT and PP analysis
Participants	440 participants with chronic bronchitis (MRC). Age 20 to 70; FEV_1 40% to 70%; at least 2 exacerbations in previous 12 months Exclusions: neoplastic disease, TB, asthma or uncompensated liver, kidney or heart disease, pregnancy Other mucoactive and anti-cough agents, oral or inhaled corticosteroids not permitted Mean age 60 years; 75% had smoking history; FEV_1 2.12 (SD 0.6) L; mean 2.7 (SD 1.3) exacerbations in past 12 months Dropouts: 89 (20%)
Interventions	3 treatment arms. Carbocysteine lysine salt monohydrate (SCMC-Lys) 2.7 g daily, placebo, and SCMC-Lys 2.7 g daily alternating 1 week active, 1 week placebo. We assessed continuous vs placebo treatment only
Outcomes	Diary scores of symptoms, exacerbations, time to first exacerbation, duration of exacerbation, days on antibiotics, adverse events
Notes	Italian. Requested SD for exacerbations for per-protocol and intention-to-treat analysis. Requested data were provided by sponsoring company. ITT analysis was done with an estimate of duration of treatment derived from the paper

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated; balanced per centre
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	20% dropout rate (89/440); dropout was higher in the intervention arm compared to the placebo arm (23% vs 16%), largely due to more participants in the intervention arm failing to comply with the trial protocol
Selective reporting (reporting bias)	Low risk	Reported main outcomes with ITT and PP analyses

Babolini 1980

Methods	Double-blind, placebo-controlled, parallel, 36 centres. PP analysis. Duration 6 months
Participants	744 outpatients with chronic bronchitis defined by MRC. Excluded if too young, too sick, additional significant disease, history of peptic ulcer, on mucolytics. 60% were over the age of 50; 73.5% were male;

Babolini 1980 *(Continued)*

	mean FEV_1 2.18 L; FEV_1 40% to 70% predicted; 64.3% smokers. 249 dropouts. Baseline groups matched. Dropout groups matched
Interventions	NAC 200 mg twice daily or placebo
Outcomes	Exacerbations, symptom scores, global assessments by participants and physicians, adverse effects, days on antibiotics
Notes	Italian. Same data also in Ferrari. SD calculated from graph. 5 or more exacerbations counted as 5. Further data requested but not yet provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Restricted' randomisation; balanced blocks
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; matching placebo, identified by code number
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	117/371 (32%) participants dropped out of the intervention arm and 132/373 (35%) participants dropped out of the placebo arm. More participants withdrew from the placebo arm due to lack of efficacy (6 vs 2) and adverse reactions (13 vs 6); other reasons were reasonably balanced
Selective reporting (reporting bias)	Low risk	None detected

Bachh 2007

Methods	Randomised, single-blind, placebo-controlled, parallel, single-centre. Follow-up 12 months, although treatment given for only 4 months
Participants	100 outpatients with smoking-related COPD. Age > 50 years; post-bronchodilator FEV_1 30% to 80% predicted; reversibility < 12%; FEV_1/FVC < 70%. Stable medications and ICS permitted at steady dose Exclusions: intolerance of NAC, continuous treatment with OCS, NAC for 3/12 or more, asthma or atopy, other respiratory diseases, NYHA Class II or greater heart failure. Non-compliance in taking medication Mean age: 61 (SD 7) years; 78% male. Mean duration of disease 6.4 years. Mean number of exacerbations in 2 years before study, 4.7. Mean FEV_1 52% (SD 10) predicted and reversibility 6% (SD3). 18/100 (18%) were using ICS No dropouts recorded
Interventions	NAC 600 mg once daily or placebo for 4 months

Bachh 2007 *(Continued)*

Outcomes	Exacerbations, hospital admissions, pulmonary function tests, adverse effects
Notes	Indian study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	High risk	Single-blind
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind; investigators not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Single-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts recorded
Selective reporting (reporting bias)	Low risk	Main outcomes reported

Boman 1983

Methods	Randomised, double-blind, placebo-controlled, parallel, run-in, multi-centre. Duration 6 months
Participants	259 outpatients with chronic bronchitis defined by MRC. Exclusion criteria: asthma, FEV_1 < 50%; other comorbidities; on antibiotics; women pregnant or trying for pregnancy. 56 dropouts. Mean age 51.9 years. FEV_1 80% predicted. 100% smokers Exacerbations in past 12 months
Interventions	NAC 200 mg twice daily or placebo
Outcomes	Exacerbations, sick leave due to exacerbations, adverse effects
Notes	Swedish. SD calculated from paper. 6 or more exacerbations counted as 6. Requested more information to calculate effect on sick days, but study authors unable to locate original material

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Done independently at each centre via a table of random numbers
Allocation concealment (selection bias)	High risk	Investigators aware of order of allocation

Boman 1983 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but may have been aware of allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind, but may have been aware of allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	High dropout rate (22%; 56/259), but numbers and reasons similar in both trial arms. All participants included in the safety analyses
Selective reporting (reporting bias)	Low risk	Main outcomes reported

Bontognali 1991

Methods	Randomised, double-blind, placebo-controlled. Duration 3 months
Participants	60 participants with chronic bronchitis recruited as inpatients; 63% male. Mean age 57 years. Admission criteria 20 mL sputum/day with history of 4 or more episodes of acute bronchitis in past 12 months and Tiffeneau index ≤ 40%. No loss to follow-up
Interventions	Cithiolone 400 mg twice daily or placebo for 1 month followed by 400 mg once daily for a further 2 months
Outcomes	Exacerbations and duration of acute exacerbations, FEV_1 and FVC, sputum viscosity, adverse effects
Notes	Italian. Surprising that no participants withdrew from the study. Huge confidence limits. Possible typographical error in paper, as SD for number of exacerbations per month is the same as for duration of exacerbations. We have used study authors' rates in comparison 01:02 and divided them by months

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	All completed study

Bontognali 1991 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Main outcomes not stated viz "efficacy"

Borgia 1981

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre. PP analysis. Duration 6 months
Participants	21 outpatients with chronic bronchitis defined by MRC and exacerbation in period before the study. Mean age 45.3 years and FEV_1 3.82 L. Exclusions not stated except FEV_1 < 40%. 2 dropped out
Interventions	NAC 200 mg twice daily or placebo
Outcomes	Exacerbations, lung function, symptom scores, clinical assessment, adverse effects
Notes	Italian. Published in Italian; therefore reliant on translation. Large differences in baseline rates for lung function

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9% dropout rate (2/21), both from the placebo arm. One participant failed to return for follow-up and the other experienced diarrhoea
Selective reporting (reporting bias)	Low risk	Main outcomes reported

Castiglioni 1986

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre (18). PP analysis. Duration 3 months
Participants	706 outpatients with chronic bronchitis defined by MRC. Mean age 56.5 years; 76% male; FEV_1 73.3% predicted; 73.5% current or former smokers. Excluded were patients younger than 18 years or older than 75; FEV_1 < 60%; severe comorbidity; prior treatment with oral corticosteroids or antibiotics and > 2 other medications. 33 dropped out

Castiglioni 1986 *(Continued)*

Interventions	Sobrerol 300 mg twice daily or placebo
Outcomes	Exacerbation rate, consumption of antibiotics and other medicines, clinical signs, laboratory data, lung function, global assessment by investigator and participant, adverse effects
Notes	Italian. Requested more information to allow determination of days on antibiotics; not yet provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Done independently at each centre with a table of random numbers to obtain balanced groups
Allocation concealment (selection bias)	High risk	Investigators aware of order of allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind; matching placebo but may have been aware of allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind but may have been aware of allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	5% dropout rate (33/706); numbers and reasons balanced between trial arms
Selective reporting (reporting bias)	Low risk	Main outcomes reported

Cegla 1988

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre. PP analysis. Duration 24 months
Participants	180 outpatients with chronic bronchitis defined by WHO Mean age 51.1 years; 64% male. Mean FEV_1 2.15 L; 36% current smokers. Excluded were patients over 60 years of age and patients with asthma, cor pulmonale, pulmonary hypertension, or polycythaemia < 60%. 23 dropped out. 4 people died
Interventions	Ambroxol retard 75 mg daily or placebo
Outcomes	Exacerbations, days sick (off work, in hospital), participant symptoms by diary card, lung function, extra medication use, assessment by investigator and participant, adverse effects
Notes	German. Written in German. Required translation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available

Cegla 1988 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	A total of 23/180 (13%) participants did not complete follow-up. 7/180 participants were excluded from the final analysis (4 in the intervention group and 3 in the placebo group). A further 16 participants were followed up for at least 6 months but dropped out before completing the trial. Reasons for loss to follow-up are not given
Selective reporting (reporting bias)	Unclear risk	Information not available

Cremonini 1986

Methods	Randomised, double-blind, placebo-controlled, parallel. Duration 3 months
Participants	41 outpatients with chronic bronchitis defined by ERS, all of whom completed the study. Exclusion criteria not stated. Mean age 60.8 years; FEV_1 58.6% predicted
Interventions	Letosteine 50 mg 3 times daily or placebo
Outcomes	Exacerbations, days off work sick, lung function. Adverse effects not evaluated
Notes	Italian. Written in Italian; therefore relying on translation. SD calculated from raw data in paper, but numbers in placebo and active groups vary (20/21 or 21/20 respectively)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias)	Low risk	All completed study

Cremonini 1986 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	Information not available

Dal Negro 2017

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre (10). Duration 12 months
Participants	467 outpatients who were current or ex-smokers aged 40 to 80 years with GOLD stage II/III and a stable therapeutic regimen for more than 8 weeks. Patients had to have experienced 2 or more acute COPD exacerbations requiring medical intervention in the previous 12 months Exclusions: pregnant, lactating mother; lack of efficient contraception in a subject with child-bearing potential; acute exacerbation of COPD within 8 weeks before inclusion; treatment with antibiotics and/or systemic steroids and/or hospitalisations within 8 weeks before inclusion; change in therapeutic regimen for COPD in the last 8 weeks before inclusion; COPD stage IV; current or past diagnosis of asthma; FEV_1 reversibility test showing change in FEV_1 > 400 mL 30 minutes after inhalation of 400 µg of salbutamol pMDI; clinically significant or unstable concurrent disease or other significant renal impairment as indicated by creatinine clearance < 25 mL/ min; active peptic ulcer; liver cirrhosis Mean age: 64.8; 74% male Dropouts: 22% in erdosteine group; 22% in placebo group
Interventions	Erdosteine 300 mg twice daily or placebo
Outcomes	Primary outcome: number of acute exacerbations Secondary outcomes: spirometry parameters, COPD symptoms, quality of life, safety and tolerability of erdosteine
Notes	RESTORE study: multi-national study including 10 European countries funded by Edmond Pharma

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An independent statistician generated a randomisation list of patient random numbers using a pseudo-random number generator. Series of 4 patients for each of the 2 strata were assigned to study sites to achieve, within each centre, a balanced number of patients treated with erdosteine or placebo in each of the 2 strata
Allocation concealment (selection bias)	Low risk	Erdosteine and placebo capsules were manufactured and provided by the sponsor. Placebo was identical in composition, shape, colour, and size but did not contain any active ingredients. Erdosteine or placebo capsules were packed identically. The investigator or anyone at the study site was prevented from knowing the allocation sequence with code labelling
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was identical in composition, shape, colour, and size but did not contain any active ingredients. Erdosteine or placebo capsules were packed identically. The investigator or anyone at the study site was prevented from knowing the allocation sequence with code labelling. The sponsor and the clinical research associate were notified if there was a clinical reason for an individual's treatment to be unmasked by the investigator

Dal Negro 2017 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specifically described in trial report, but in clinical trials, record outcome assessors described as blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Approx 20% withdrew from both arms (50/228 from the intervention arm and 52/239 from the placebo arm) for similar reasons, but ITT analysis conducted including over 90% of participants in both arms
Selective reporting (reporting bias)	Low risk	Several outcomes of interest reported narratively as 'no difference' in publication, but study authors supplied required information upon request

De Backer 2013

Methods	Randomised, double-blind, placebo-controlled, cross-over. Duration 3 months
Participants	12 outpatients with GOLD stage II or III COPD, age ≥ 40, smoking history at least 10 pack-years but now smoke free, presence of COPD symptoms. 9 men and 3 women with mean age 65, 56 pack-years, and FEV_1 65%. All completed the study. Exclusions: recent exacerbation; allergy to or prior treatment with NAC; PKU; untreated peptic ulcer; organ insufficiency; ongoing treatment with oral, IV, or IM steroids; pregnancy or breastfeeding; treatment with oral cephalosporin
Interventions	NAC 600 mg 3 times daily or placebo
Outcomes	Measured at baseline and at end of each 3/12 treatment period: spirometry, PEFR, raw NO, specific airway resistance from plethysmography, CT to look at airway geometry, serum glutathione, enzymes, SGRQ, ABG
Notes	Belgian. Funded by an imaging company and a pharmaceutical company Dr Backer works for FluidDA, a functional respiratory imaging company, contracted by Zambon, manufacturer of NAC Responder analysis. Did not report on spirometry or SGRQ results for treatment groups as a whole. These have been requested

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Computer-generated randomisation list used; no further details
Allocation concealment (selection bias)	High risk	Cross-over trial. Trial lasted from August 2009 to June 2012 for only 12 participants. No details on allocation or concealment procedures reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were their own controls. No information about similarity of NAC and placebo
Blinding of outcome assessment (detection bias) All outcomes	High risk	Cross-over trial with no washout period. Possible practice effects. Unsure how blinded investigators were
Incomplete outcome data (attrition bias)	Low risk	All participants completed the study

De Backer 2013 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	High risk	Reported responder analysis. Did not report on spirometry or SGRQ results for treatment groups as a whole

Decramer 2005

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre. ITT analysis. Duration 3 years
Participants	523 outpatients with smoking-related COPD. Age 40 to 75 years; post-bronchodilator FEV_1 40% to 70% predicted; reversibility < 12% and 200 mL; FEV_1/FVC 88% for men and 89% for women; history of at least 2 exacerbations during 2 years before enrolment Exclusions: intolerance of NAC, continuous treatment with oral steroids, NAC for 3/12 or longer, asthma or atopy, other respiratory diseases, NYHA Class II or greater heart failure, GI disease, likely LTOT or lung transplant, alpha 1 antitrypsin deficiency, enrolment in rehab or other study 3 months before this study. ICS permitted, although steady dose recommended Mean age 62 (SD 8) years; 79% male; FEV_1 1.65 (SD 0.38) L; 57% (SD 9) predicted; 46% current smokers; 70% used ICS Yearly exacerbation rate (control group) 2.5 (SD 0.9) events Dropouts: 70 (27%) in NAC group and 99 (37%) in placebo group (P = 0.018)
Interventions	NAC 600 mg daily vs placebo
Outcomes	Yearly reduction in lung function and exacerbation rate Secondary endpoints: quality of life (SGRQ), cost utility Planned subgroup analyses - by baseline ICS dose and disease severity
Notes	European. BRONCUS study Cost utility will be reported in another publication Data from mixed-effects model used in this study have been provided by Professor De Cramer for total SGRQ scores. Change on NAC was -2.31 and on placebo -3.71 Add these to baseline (using baseline SD) 36.7 (16) and 36.3 (15) to get total SGRQ at end of study to enter into RevMan

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Allocation concealed from study investigators
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; identical placebo and active tablets
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind; investigator unaware of treatment allocation

Decramer 2005 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	High and unbalanced dropout; 70/256 (27%) and 99/267 (37%) withdrew from mucolytics and placebo, respectively. A greater number of placebo participants withdrew consent (26 vs 13), experienced an adverse event leading to withdrawal (26 vs 19), or experienced worsening of disease/lack of efficacy (6 vs 2)
Selective reporting (reporting bias)	Low risk	None detected

Ekberg-Jansson 1999

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre (41). PP analysis. Duration 6 months
Participants	637 outpatients with chronic bronchitis defined by MRC 1 exacerbation in previous winter. Average age 58 years; 61% male; mean FEV_1 73% predicted; 100% current smokers or ex-smokers. Exclusions: females of fertile age, FEV_1 < 40% predicted, significant reversibility, unstable non-respiratory disease, other respiratory disease, atopy, peptic ulcer, lactose intolerance or daily purulent sputum. 134 dropped out
Interventions	N-isobutyrylcysteine (NIC) 300 mg twice daily or placebo
Outcomes	Time to first exacerbation, exacerbation rate, days sick (judged by participants and investigators), lung function, adverse effects
Notes	European including British. New agent-free thiol donor derivative of NAC

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	72/316 (23%) dropped out of the intervention arm and 62/321 (19%) dropped out of the placebo arm. There were more adverse events leading to discontinuation in the intervention arm (42 vs 25), and more dropouts in the placebo arm were classified as "other reasons" (34 vs 22)
Selective reporting (reporting bias)	Low risk	Reported on main outcomes

Fukuchi 2016

Methods	Randomised, double-blind, placebo-controlled, parallel. Duration 12 months
Participants	408 outpatients between 20 and 85 years of age with smoking history, post-bronchodilator ratio of FEV_1 to forced vital capacity (FVC) < 70%, and FEV_1 < 80% predicted in the screening Exclusions: history of COPD exacerbation within 7 days before the start of oral administration of study drugs; history of lung transplantation, pneumonectomy, or lung volume reduction surgery; clinically severe disease (e.g. pulmonary tuberculosis) Dropouts: 15% in lysozyme group; 17% in placebo group
Interventions	Lysozyme 90 mg 3 times daily or placebo
Outcomes	Primary outcome: prevention of COPD exacerbation (as assessed by exacerbation rate and time to first exacerbation) Secondary outcomes: respiratory function assessed by spirometry, health status assessed by CAT
Notes	Japanese. This study was conducted with funds from Aska Pharmaceutical Co., Ltd.; Nippon Shinyaku Co., Ltd.; and Eisai Co., Ltd. Two patients were withdrawn from the study before the start of oral administration

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	After the screening period, patients were randomly assigned to lysozyme or placebo treatment in a ratio of 1:1. Correspondence with trial authors confirmed that "independent statisticians from sponsors made a randomized sequence. The randomization sequence was made by permuted block method with variable block size of block sizes 2 and 4 and equal randomization ratio, using SAS"
Allocation concealment (selection bias)	Low risk	Correspondence with trial authors confirmed "based on the randomized sequence, the study drug was placed in a box and sealed"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study used a "matching placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Correspondence with trial authors confirmed that outcome assessors remained blind to group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	31/202 (15%) dropped out of the intervention arm and 35/204 (35%) dropped out of the placebo arm. Correspondence with trial authors confirmed that reasons for withdrawal were balanced between trial arms
Selective reporting (reporting bias)	Low risk	Quality of life score not reported numerically in published trial report but supplied by trial authors on request

Grassi 1976

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre (6). PP analysis. Duration 6 months

Grassi 1976 *(Continued)*

Participants	80 outpatients with chronic bronchitis defined by American and British criteria. 11 dropped out. Mean age 60.9 years; 80% male
Interventions	NAC 600 mg daily or placebo for 3 days per week
Outcomes	Exacerbations, clinical symptoms (3 months), sputum characteristics, adverse effects
Notes	Italian. SD calculated from paper. 3 or more exacerbations counted as 3. 1 to 2 exacerbations counted as 1.5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5/40 (13%) dropped out of intervention arm and 6/40 (15%) of placebo arm. A further 4 were excluded (3 placebo and 1 intervention) due to ineffectiveness of treatment. Reasons for 11 dropouts were not given
Selective reporting (reporting bias)	Low risk	Main outcomes reported

Grassi 1994

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre. PP analysis. Duration 3 months
Participants	135 outpatients with chronic bronchitis with at least 2 exacerbations previous winter randomly assigned to 1 of 3 treatments. Participants aged 40 and 75, mean age 61.8 years; chronic bronchitis for at least 5 years; FEV_1 56.7% predicted; 76% smokers For this analysis, n = 87. 4 dropped out
Interventions	Carbocysteine-sobrerol 1 dose daily, placebo 1 dose daily, or alternating active-placebo for 10 days each, for 3 months. 1 treatment group was intermittent; this is not included in the analysis
Outcomes	Exacerbations, symptoms, sputum characteristics
Notes	Italian. Published in Italian; therefore relying on translation. SD calculated from paper

Risk of bias

Bias	Authors' judgement	Support for judgement

Grassi 1994 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/45 (7%) from the intervention group and 1/42 (2%) from the placebo group dropped out. Reasons for withdrawal from the intervention group included refusal of treatment, non-attendance at follow-up, and an adverse event. The only participant who dropped out of the placebo group refused treatment
Selective reporting (reporting bias)	Low risk	Main outcomes reported

Grillage 1985

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre (17). PP analysis. Duration 6 months
Participants	109 general practice patients with chronic bronchitis defined by MRC, reversibility < 20%. Exclusions: severe hepatic or renal impairment or peptic ulcer; taking mucolytics or steroids. Participants were over 40 years of age; mean PEFR 232 L/min, with episodes of bronchitis in previous winters. 11 dropped out, including 2 who died
Interventions	Carbocysteine 750 mg 3 times daily or placebo
Outcomes	Exacerbations, lung function, adverse effects
Notes	British. Excluded from original review, but with new comparison, "pts with no exacerbations" can now be included

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; matching placebo

Grillage 1985 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6/54 (11%) dropped out of the intervention arm: 3 due to adverse events, 2 due to non-compliance, and 1 moved to another area. 3/55 (5%) dropped out of the placebo arm: 2 due to adverse events, 1 due to inefficacy of the trial medication
Selective reporting (reporting bias)	Low risk	Reported on main outcomes

Hansen 1994

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre (6). 4-week run-in. PP analysis. Duration 5 months
Participants	153 outpatients with chronic bronchitis defined by MRC. At least 2 exacerbations in past year; $FEV_1 \geq$ 50% predicted; < 20% reversibility. 100% had smoked. Exclusions were those with atopy or heart disease and on long-term antibiotics. Mean age 51.4 years; 43% male. Mean FEV_1 2.34 L; 24 dropped out
Interventions	NAC 600 mg twice daily or placebo
Outcomes	Exacerbations, subjective symptom scores, global well-being, lung function, adverse effects. Sick days not assessed
Notes	Danish

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation in blocks of 4 provided by third party
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	16/75 (21%) dropped out of the intervention arm and 8/78 (10%) from the placebo arm. Reasons for dropout not reported
Selective reporting (reporting bias)	Low risk	Main outcomes reported

Jackson 1984

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre (16). PP analysis. Duration 3 months
Participants	155 general practice patients with chronic bronchitis defined by MRC. 88% had smoked. Exclusions were those with other serious respiratory disease or peptic ulcer and those on long-term antibiotics or requiring mucolytics. Mean age 63 years; 67% male. 34 dropped out
Interventions	NAC 200 mg 3 times daily or placebo
Outcomes	Exacerbations, subjective symptom scores, clinical signs, radiological appearance, global well-being, adverse effects
Notes	British. Excluded from original review, but with new comparison, "pts with no exacerbations" can now be included

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	22% overall dropout rate (34/155). 4 participants withdrew from the intervention arm due to adverse events and 5 from the placebo arm. Other reasons for withdrawal from each arm not given
Selective reporting (reporting bias)	Unclear risk	None detected

Johnson 2016

Methods	Randomised, double-blind, placebo-controlled, parallel. Duration 8 weeks
Participants	51 outpatients with chronic cough and sputum production. Principal eligibility criteria were as follows: (1) ratio of post-bronchodilator $FEV_1/FVC < 0.70$ along with $FEV_1 < 65\%$ predicted; (2) age > 40 years and < 85 years; (3) current or past history of cigarette smoking of at least 10 pack-years; (4) no COPD exacerbation in the last 4 weeks; (5) presence of chronic bronchitis Exclusions: (1) primary clinical diagnosis of asthma; (2) uncompensated heart failure; (3) cirrhosis with ascites and edema; (4) estimated glomerular filtration rate 30 mL/min/1.73 m^2; (5) use of long-acting nitrates; (6) inability to provide informed consent Mean age 70 years; average FEV_1 40% predicted

Johnson 2016 *(Continued)*

	Dropouts: 15% in NAC group; 8% in placebo group
Interventions	NAC 1800 mg twice daily or placebo
Outcomes	Primary outcome: change in total score of the SGRQ Secondary outcomes: changes in the 3 domains of the SGRQ, CBSAS, SF-36, lung function with post-bronchodilator spirometry
Notes	American. Funded by the Minnesota Veterans Medical Research and Education Foundation, the HealthPartners Institute of Education and Research, and the University of Minnesota Graduate School. Trial terminated due to safety concerns before enrolment completed. Unclear what impact this had on results reported. Study authors conducted an analysis to determine the probability of a statistically significant difference in SGRQ had the trial continued, and concluded that had a mid-study futility analysis been incorporated into the protocol, this result in itself would have terminated the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	At each site, patients were randomized 1:1 to active drug or placebo in permuted blocks of size 2. Research pharmacists at each site were the only study personnel with access to the randomisation list
Allocation concealment (selection bias)	Low risk	Research pharmacists at each site were the only study personnel with access to the randomisation list; they assigned treatment accordingly. All other study personnel and study patients were fully blinded to the allocation arm
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo tablets were indistinguishable from active drug in terms of appearance, effervescence, taste, and odour
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All study personnel and study patients were fully blinded to the allocation arm. The study team was unblinded to efficacy outcomes only after the decision had been made to terminate the trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/27 (15%) participants in the intervention arm did not complete the trial; 2/24 (8%) participants in the placebo arm did not complete. One placebo participant was unable to make the follow-up visit; the remainder did not complete due to early trial termination
Selective reporting (reporting bias)	Low risk	All planned outcomes of interest in this review reported fully. SGRQ only outcome listed on clinical trials record

Malerba 2004

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre (26). ITT and OT. Duration 12 months
Participants	242 participants with COPD (ATS definition) and chronic bronchitis. Age 40 to 75; FEV_1 60% to 80% (GOLD stage IIA); pathological chest auscultatory findings; at least 1 exacerbation in previous 12 months Exclusions: CF, bronchiectasis, asthma, centrilobular emphysema, peptic ulcer or liver, kidney or heart insufficiency

Malerba 2004 *(Continued)*

	Other mucoactive and anti-cough agents, OCS, or ICS not permitted. ICS withdrawn at least 4 weeks before study Mean age 60 years; 75% had smoking history; FEV_1 2.12 (SD 0.6) L; mean 2.7 (SD 1.3) exacerbations in past 12 months Dropouts: 34 (16%)
Interventions	Ambroxol 75 mg twice daily or placebo
Outcomes	Exacerbations over first 6 months (winter period) and at 12 months Secondary: cough intensity and frequency, difficult expectoration, dyspnoea, days on antibiotics, number of working days lost, number of days of hospitalisation
Notes	Italian. AMETHIST study Post hoc analysis on participants with more severe condition

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	14% dropout rate (34/242), but only 3% excluded from intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Main outcomes reported; some post hoc analysis

McGavin 1985

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre (26). PP analysis. Duration 5 months
Participants	244 participants entered the study, with 200 participants randomly assigned. 181 randomly assigned appropriately (others ineligible or untraceable). Chronic bronchitis defined by MRC; 1 or more exacerbations per year for the past 3 years; FEV_1 < 50% and FEV_1/FVC < 70% predicted. Mean FEV_1 0.86 L. Mean age 63.4 years; 85% male. 99% current smokers or ex-smokers. 148 completed 5 months of treatment
Interventions	NAC 200 mg 3 times daily or placebo
Outcomes	Exacerbations, days of antibiotics, days in bed, FEV_1 and VC, adverse effects

McGavin 1985 *(Continued)*

Notes	British. BTS research committee. Mean exacerbation rate given by study authors does not agree with what we calculated from their raw data. Have used authors' rates. Have used SE from body of text (same value reported in abstract as SD). For post-treatment FEV_1, SD estimated from baseline data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	52/200 (26%) randomised participants did not complete the trial. 14 were found to be 'ineligible' (10 in the intervention group and 4 in the placebo group), and a further 5 were lost from the intervention group through "administrative error". Of the remaining eligible participants, 13 dropped out from the intervention group and 20 from the placebo group. The imbalance in numbers is largely due to more participants in the placebo group dropping out due to being "too ill"
Selective reporting (reporting bias)	Unclear risk	Outcomes not stated clearly, viz "the effect" of ...

Meister 1986

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre (54). Duration 6 months
Participants	252 outpatients with chronic bronchitis defined by WHO. At least 1 exacerbation in the past winter. 10 patients with asthma and chronic bronchitis were included. Exclusions: those who had received at least 14 days of antibiotics for chronic bronchitis in the past 6 months; pregnancy. Average age 57.2 years; 59% male. Average PEFR 303 L/min. 88% had smoked. 71 dropped out
Interventions	NAC 300 mg twice daily or placebo
Outcomes	Exacerbations, days sick, concomitant treatment, adverse effects
Notes	German. Provided by Zambon. Not published

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available

Meister 1986 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	38/128 (30%) dropped out of the intervention group and 33/124 (27%) dropped out of the placebo group. Reasons were given and were balanced between arms; the trialist reported that sensitivity analysis suggested no important differences between those who dropped out and those who remained in the study. Results are reported for those who completed, rather than results of an intention-to-treat analysis. High attrition for a trial of 6 months' duration, so judged to be at high risk
Selective reporting (reporting bias)	High risk	Not published

Meister 1999

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre (19). PP and ITT analyses reported. Duration 6 months
Participants	246 outpatients with chronic bronchitis as defined by WHO and FEV_1 > 50% predicted. 215 completed 6 months. At least 1 exacerbation in the past winter. Exclusions: those who had antibiotics in past 2 months, peptic ulcer disease, neoplasia, allergy to essential oils, pregnancy, lactation, severe concomitant disease. AveraMoretti 2004: age 57 years, 44% male. Mean FEV_1 78% predicted. 55% had smoked. 42 dropped out
Interventions	Myrtol 300 mg 3 times daily or placebo
Outcomes	Exacerbations, number of exacerbations requiring antibiotics, well-being, adverse effects
Notes	German. Abstract provided by Douglas Pharmaceuticals. Full paper (English) provided by Pohl-Boskamp. PP analysis used in review (participants completing 6 months). Results of ITT analysis consistent with PP analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias)	Low risk	Double-blind; matched placebo

Meister 1999 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	260 participants received study medication at least once, of whom 42 (16%) discontinued the study prematurely. The ITT population comprised those who has received study medication for at least 1 month. 12/122 (10%) dropped out of the intervention ITT group and 19/124 (15%) from the placebo ITT arm. Reasons were balanced
Selective reporting (reporting bias)	Low risk	Reported on main outcomes: both PP and ITT

Moretti 2004

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre (9). PP analysis reported. Duration 8 months
Participants	155 outpatients with COPD defined by ERS. Age 25 to 85 years; 1 or more exacerbations in previous winter; FEV_1 < 70% predicted; CXR no acute lung disease; smoking history > 20 pack-years; stable and at least 4 weeks since last exacerbation Exclusions: continuous treatment with oral steroids or expectorants; rapidly progressive bronchial disease; serious comorbidity; asthma; known poor compliance Mean age 67 years; 80% male; 33% smokers; FEV_1 after salbutamol 1.68 L (SD 0.31) in erdosteine group and 1.59 L (0.29) in placebo group Dropouts: 31/155 (20%). Equal in both groups and similar reasons. 63 in mucolytic group and 61 in placebo group completed
Interventions	Erdosteine 300 mg twice daily or placebo
Outcomes	Exacerbation frequency, duration, hospitalisation, lung function, 6-minute walk test, quality of life (SGRQ), pharmacoeconomic analysis
Notes	Italian. EQUALIFE study Mucolytic group had (insignificantly) more males and better lung function at baseline

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind

Moretti 2004 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	16/79 (20%) dropped out of the intervention group and 15/76 (20%) dropped out of the placebo group. Reasons were balanced
Selective reporting (reporting bias)	Low risk	Reported all primary outcomes

Nowak 1999

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre (10 centres). PP analysis. Duration "long term" means 8 months
Participants	313 outpatients with COPD (diagnostic criteria not clear). Mean age 57 years; 60% male. Mean FEV_1 60% predicted. 18 dropped out
Interventions	NAC 600 mg daily or placebo
Outcomes	Exacerbations, severity of exacerbations, time to first exacerbation, days sick, lung function, participant symptoms, adverse effects
Notes	European. COPD, not chronic bronchitis. BREATHE study. Published in abstract form only. Zambon provided more information. Study never published in full

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	12/159 (8%) dropped out of the intervention arm and 6/154 (4%) dropped out of the placebo arm. Reasons for dropout not reported, but overall low rate of attrition
Selective reporting (reporting bias)	High risk	Information not available

Olivieri 1987

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre (13). PP analysis. Duration 6 months
Participants	240 outpatients with chronic bronchitis defined by MRC. At least 3 exacerbations in previous year or pathological auscultatory assessment or reduction of 15% to 40% in FEV_1. Exclusions: patients with asthma, FEV_1 < 40% predicted, peptic ulcer or other serious comorbidity, pregnancy, long-term antibiotics or mucolytics. 26 dropped out
Interventions	Ambroxol retard 75 mg or placebo daily
Outcomes	Exacerbations, courses of antibiotics, days sick, FEV_1, VC, symptoms, auscultatory findings, physician and participant global assessments, laboratory data, adverse effects
Notes	Italian. We suspect that what is reported as SD in the paper is in fact SE (using t statistic and P values). We wrote to study authors for clarification. We received no reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-randomised
Allocation concealment (selection bias)	Unclear risk	Each centre provided with a list
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	11/121 (9%) dropped out of the intervention arm and 15/119 (13%) dropped out of the placebo arm. More participants in the placebo group "failed to return" (9 vs 3) or experienced "inefficacy" (3 vs 1) or an adverse reaction leading to withdrawal (2 vs 0). More participants in the intervention group withdrew due to "poor collaboration" (2 vs 0) or leaving the department (3 vs 1)
Selective reporting (reporting bias)	Low risk	PP and ITT analyses of all main outcomes

Parr 1987

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre. PP analysis. Duration 6 months
Participants	526 general practice patients with chronic bronchitis defined by MRC, with at least 1 exacerbation in past 12 months. Exclusions: other significant respiratory disease, active peptic ulceration, severe heart failure, continuous therapy with antibiotics or mucolytics. 204 dropouts. Mean age 63 years; 66% male; 86% had smoked
Interventions	NAC 200 mg 3 times daily or placebo

Parr 1987 *(Continued)*

Outcomes	Exacerbations, days off work, adverse effects
Notes	British. Pharmaceutical company trial. Large number of dropouts, although seemed matched. SD calculated from raw data in paper. More data needed to calculate days sick

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned in blocks of 4
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; interventions identical
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	204/526 (39%) did not complete all follow-up over the 6-month follow up period. 49 missed 1 or more assessment but were subsequently followed up. Two participants remained lost to follow-up. 153 dropped out; 79/258 (31%) dropped out of the intervention group and 75/268 (28%) dropped out of the placebo group. Reasons for dropout were reasonably balanced, although more participants withdrew from the intervention arm due to "lack of efficacy" (15 vs 6)
Selective reporting (reporting bias)	Unclear risk	No specific outcomes stated

Pela 1999

Methods	Randomised, open, placebo-controlled, parallel, multi-centre (5). Duration 6 months. PP analysis
Participants	169 outpatients with COPD (defined by ATS and ERS); aged 40 to 75 years; FEV_1 < 70% predicted; reversibility < 12% Exclusions: lung cancer, cardiomyopathy, metabolic disease, renal failure, other severe disease. Mean age 66 years; 76% male; mean FEV_1 1.49 L; 58% predicted; 28% current smokers. 6 dropped out
Interventions	NAC 600 mg daily or placebo
Outcomes	Exacerbations, exacerbation severity, days sick, participant preference, lung function
Notes	Italian study. Open study. COPD, not chronic bronchitis

Risk of bias

Bias	Authors' judgement	Support for judgement

Pela 1999 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	High risk	Investigators aware of order of allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2/85 (2%) dropped out of the intervention group and 4/84 (5%) from the standard care group. Reasons were balanced
Selective reporting (reporting bias)	Low risk	Reported on main outcomes

Petty 1990

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre. Duration 2 months. ITT analysis
Participants	367 outpatients with stable chronic bronchitis defined by ATS were randomly assigned. Required pre-bronchodilator FEV_1 < 75% predicted. 79 dropouts (33 in mucolytic group and 46 in placebo group). Mean age 65 years; 70% male; mean FEV_1 44.5% predicted. Exclusions: pregnant or lactating, allergic to iodine, comorbidity that would confound response or compliance, asthma, exacerbation in past month, using antibiotics or anticholinergics
Interventions	Iodinated glycerol 30 mg, 2 tabs 4 times a day, or identical-looking placebo
Outcomes	Investigator assessment of symptoms; participant evaluation of symptoms; global assessment at weeks 0, 4, and 8; frequency of bronchodilator use; number and duration of acute exacerbations; frequency of concomitant medications; adverse experiences Dropouts assessed at weeks 4 and 8
Notes	American. Requested more information from study author, but study author was unable to provide. Pharmaceutical company (Wallace) approached. No reply. No significant differences (reported) between groups in exacerbation rates; however, significantly fewer days sick in treatment group. We estimated sample SD from t statistic and pooled t formula and assumed equal variances to arrive at an estimate for SD of 18.8

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Information not available

Petty 1990 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; matched placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	35/182 (19%) dropped out of the intervention arm and 50/185 (27%) from the placebo arm. Reasons were relatively balanced, with the exception of withdrawals due to adverse events (10 in the intervention group vs 24 in the placebo group), which accounts for the imbalance in numbers
Selective reporting (reporting bias)	Low risk	None detected

Rasmussen 1988

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre (9). PP analysis. Duration 6 months
Participants	116 outpatients with chronic bronchitis defined by MRC. At least 1 exacerbation previous winter. 100% had smoked. Mean age 58.9 years; 57% male; average PEFR 305 L/min. 25 dropped out
Interventions	NAC 300 mg twice daily or placebo
Outcomes	Exacerbations, days sick evaluated by days on sick list and by participant diaries, adverse effects
Notes	Swedish

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation in blocks of 4
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	15/59 (25%) dropped out of the intervention group and 10/57 (18%) from the placebo group. Reasons were reasonably balanced between arms

Rasmussen 1988 *(Continued)*

Selective reporting (reporting bias)	Low risk	Main outcomes reported

Roy 2014

Methods	Randomised, single-blind, placebo-controlled, parallel, single-centre. PP analysis. Duration 6 months Followed up every month
Participants	80 outpatients age > 40, stable mild to moderate COPD, smoking history at least 10 pack-years. Exclusions: those with asthma, lung cancer, cardiomyopathy, LVRS or transplant, or on LTOT or corticosteroids. Mean age 61; 89% male. Total 20 dropouts, evenly matched between groups
Interventions	NAC 600 mg twice daily or placebo. Both groups received a bronchodilator Deriphylline Retard 150 mg in addition
Outcomes	Symptoms (cough, dyspnoea, sputum), spirometry, Hb, adverse events
Notes	Indian Funding source not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	No details on this, except it was a "simple method"
Allocation concealment (selection bias)	High risk	Single-blind study; few details on allocation or concealment of sequence given
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details on match between placebo and NAC, or on who performed measurements; sIngle-blind
Blinding of outcome assessment (detection bias) All outcomes	High risk	SIngle-blind study
Incomplete outcome data (attrition bias) All outcomes	High risk	25% dropout rate (20/80); numbers and reasons per arm not given
Selective reporting (reporting bias)	Unclear risk	Spirometric data reported in units that read "total count"

Schermer 2009

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre (44 general practices). Duration 3 years. ITT and PP analyses

Schermer 2009 *(Continued)*

Participants	192 (in study arms NAC and placebo, each n = 96) GP outpatients with chronic bronchitis or stable COPD between ages of 35 and 75. Current or former smokers with chronic dyspnoea, sputum, and cough for at least 3 consecutive months in previous 2 years; post-bronchodilator FEV_1 < 90% and/or post-bronchodilator FEV_1/FVC ratio < 0.88 for men and < 0.89 for women Exclusions: FEV_1/FVC ratio < 0.4 and/or history of asthma, allergic rhinitis, or eczema 84 dropouts (44 in mucolytic group and 40 in placebo group). Mean age 59 years; 73% male. Mean post-bronchodilator FEV_1 2.15 L (62% predicted). 53% were still smoking. 22% had chronic bronchitis with no obstruction: 14% mild, 47% moderate, and 17% severe COPD. Mean CRQ score 4.84; baseline exacerbation rate mean 0.88 per year/median 0.5 Participants well matched at baseline. High dropout rate. Generally low exacerbation rates, except small number of participants who experienced very frequent exacerbations
Interventions	3 arms, double-dummy (tablet and inhaler). NAC 600 mg effervescent tablet daily vs fluticasone 500 µg twice daily vs placebo. This review included only NAC vs placebo arms. 2 weeks of pretreatment with prednisone 30 mg daily
Outcomes	Primary outcomes: rates of exacerbation and disease-specific quality of life, as measured by CRQ Other outcomes: lung function, hospitalisation
Notes	Netherlands

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	List generated by independent statistician
Allocation concealment (selection bias)	Low risk	Neither participants nor investigators aware of allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-dummy
Incomplete outcome data (attrition bias) All outcomes	High risk	44% dropout rate (44/96 and 40/97 dropped out on mucolytics and placebo, respectively). Reasons and numbers are balanced but high rate overall leads to judgement of high risk
Selective reporting (reporting bias)	Low risk	None detected

Tse 2013

Methods	Randomised, double-blind, placebo-controlled, parallel. 1 hospital centre. Duration 1 year 4-week run-in period; randomisation, then follow-up at 16, 32, and 48 weeks Analysis ITT

Tse 2013 *(Continued)*

Participants	133 outpatients aged 50 to 80 with stable COPD (FEV_1/FVC < 0.7) recruited, 120 randomised. Exclusions: co-existent pulmonary disease, LTOT, BiPAP, severe dyspnoea, poor reliability or compliance. Mean age 71; 93% male; 23% current smokers 18% GOLD 1, 40% GOLD 2, 34% GOLD 3, 8% GOLD 4. Median of 2 exacerbations in past year. Groups well matched at baseline. 12 dropouts - 6 in each group
Interventions	NAC 600 mg twice daily or placebo
Outcomes	Primary: small airways parameters $FEF_{25\%-75\%}$, FOT, IC, spirometry Secondary: exacerbation rate, mMRC dyspnoea scale, SGRQ, 6MWD
Notes	Chinese (Hong Kong). HIACE study. Funded by pharmaceutical company Funding from local hospital research fund. Zambon provided NAC and placebo. 1 study author (Dr Ratieri) employed by Zambon

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No detail on this
Allocation concealment (selection bias)	Unclear risk	Not well described: "randomisation and allocation details known only to a third party"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	NAC and placebo "identical in appearance"; "patients and investigators blinded to treatment allocation during the study". Compliance assessed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Patients and investigators blinded to treatment allocation during the study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	10% dropout rate (12/120) after randomisation. Flow chart of dropout numbers provided and reasons relatively balanced
Selective reporting (reporting bias)	Low risk	All major outcomes reported in detail

Worth 2009

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre (11 centres; 4 GPs and 7 specialists). ITT analysis Duration 6 months over winter
Participants	220 outpatients aged 40 to 80 with moderate or severe COPD defined by GOLD. 30% > FEV_1 < 70%, with reversibility below 15%. All were smokers or ex-smokers. Mean age 62.3 years; 64% were male. Mean FEV_1 1.61 L (54.7% predicted). Exclusions: severe medical conditions such as bronchial carcinoma, MI, alcoholism, or heart failure. Unclear how many participants finished the study Groups well matched at baseline. Compliance said to be 'good' in all participants

Worth 2009 *(Continued)*

Interventions	Cineole 2 × 100 mg 3 times daily (total 600 mg) or placebo
Outcomes	Primary outcome: exacerbations - number, severity, duration Secondary outcomes: lung function, dyspnoea, quality of life (SGRQ), adverse effects Primary outcomes, dyspnoea, and adverse effects assessed at each visit. Lung function assessed at 0, 3, and 6 months. Quality of life assessed at 0 and 6 months
Notes	German

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Apart from an indication of stratification by site, no details given on randomisation methods
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants instructed to take medication a half hour before meals to avoid the smell of cineole. Active and placebo capsules looked identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details on dropouts
Selective reporting (reporting bias)	Low risk	None apparent

Xu 2014

Methods	Randomised, double-blind, placebo-controlled, parallel. Duration 6 months
Participants	84 outpatients over 20 years of age with chronic bronchitis as defined by the MRC, or COPD as defined by criteria of the ATS, GOLD, ERS, or WHO Exclusion criteria: not known Dropouts: no dropouts in either arm
Interventions	NAC 600 mg twice daily or salmeterol/fluticasone propionate alone
Outcomes	FEV_1/FVC, FEV_1 % predicted, PEF% daily variation change, arterial blood gas analysis index (PaO_2 and $PaCO_2$)
Notes	Study published in Chinese. Funded by Jilin provincial science and technology department

Risk of bias

Xu 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as "randomised"; no other details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	No description of placebo or blinding; assume open-label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of placebo or blinding; assume open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	All stated outcomes of interest to this review reported numerically, but no published protocol or trial registration identified

Zheng 2008

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre (22 centres). Duration 1 year. ITT analysis
Participants	709 outpatients with stable COPD defined by GOLD criteria with post-bronchodilator FEV_1/FVC ratio < 0.7 and FEV_1 between 25% and 79% predicted. Patients between ages of 40 and 80 with history of at least 2 COPD exacerbations in previous 2 years. Clinically stable in past 4 weeks. 91 dropouts (48 in mucolytic group and 43 in placebo group). Mean age 65 years; 78% male; mean FEV_1 1.09 L (44.5% predicted). 75% had ever smoked. 49% were GOLD 2, 39% GOLD 3, and 12% GOLD 4. Mean SGRQ was 42. Exclusions: asthma, non-COPD respiratory disorders, LVRS or transplant or other conditions that would interfere with the study, those on LTOT or pulmonary rehabilitation or on OCS, pregnancy or lactating. Patients involved in another investigational drug trial in past 12 weeks were also excluded 18% of intervention group and 15% of placebo group were on ICS
Interventions	Carbocysteine 1500 mg daily (2 × 250 mg 3 times daily) orally or placebo
Outcomes	Primary endpoint: exacerbation rate (defined by Anthonisen) Secondary endpoints: co-variance-adjusted exacerbation rate, quality of life (SGRQ), lung function, arterial oxygen saturation
Notes	Chinese. Main PEACE study. Financial support from Kyron Pharmaceutical, Japan *Lancet* report for main PEACE study describes 709 participants from 22 centres in China. Another 2 references to PEACE study from Japan (Tatsumi 2007a; Tatsumi 2007b). Both refer to same sample of 142 patients - 70 in control group and 72 in study group. Have written to Dr Zhong to ask if a substudy of main PEACE study was a different study
Risk of bias	

Zheng 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated randomisation list"
Allocation concealment (selection bias)	Low risk	"Neither the investigator nor the patient knew the group allocation"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The placebo was identical to the drug in appearance labelling and packaging"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Statistical analysis done without awareness of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	13% dropout rate (48/353 and 43/354 withdrew from mucolytics and placebo, respectively). Some imbalance noted in the reasons for dropout; a greater number of intervention participants dropped out due to "no compliance or lack of consent" (30 vs 16), whereas more placebo participants were lost to follow-up (21 vs 10). Analyses performed on an intention-to-treat basis
Selective reporting (reporting bias)	Low risk	None apparent

Zheng 2014

Methods	Randomised, double-blind, placebo-controlled, parallel, multi-centre (34 centres). Duration 1 year 2 week run-in period; then randomisation and visits at 1, 2, 6, 9, and 12 months. Analysis conducted on "patients who received at one dose of study drug, and had at least one visit assessment after randomisation" This ended up being 482 in each group (total 964). Completers totaled 763. Methods for handling missing data not outlined
Participants	From 1297 screened, investigators enrolled 1006 outpatients aged 40 to 80 with moderate to severe COPD (FEV_1 < 30% to 70% predicted and ratio < 0.7). These were stratified by previous regular use of ICS at baseline (500 to 2000 µg/day of beclomethasone or equivalent). Exclusions: bronchial asthma, LTOT ≥ 12 hours per day or pulmonary rehabilitation, major comorbidity, poor reliability or compliance. Ratio of ICS users to ICS naïve participants was set at about 4:6 Groups were well matched at baseline. Mean age 66 years; 82% male; 76% ever smokers; mean FEV_1 49% predicted. 46% GOLD 2, 53% GOLD 3, and 1% GOLD 4. 243 dropouts - 124 in treatment group and 119 in placebo group - with main reasons being loss to follow-up and adverse events. Provided analysis of dropouts (N = 243) vs completers (N = 763) - similar among the 2 groups
Interventions	NAC 600 mg twice daily or placebo
Outcomes	Primary: exacerbation rate in 1 year, exacerbation duration Secondary: time to first exacerbation, time to recurrent exacerbation, number of participants requiring systemic corticosteroids or antibiotics or use of SABA rescue medication, SGRQ (Chinese version), spirometry, adverse events (including hospitalisation or death)

Zheng 2014 *(Continued)*

Notes	Chinese. PANTHEON study. Funded by a pharmaceutical company (Hainan Zambon Pharmaceutical). Study authors had full access to all data and were involved in data interpretation and preparation of manuscript in collaboration with sponsor. Corresponding authors had final responsibility for decision to submit for publication Dr Zheng provided Appendix, as well as further data on exacerbation rates, SQRG scores, and spirometry

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation conducted using a pre-determined computer-generated randomisation list provided by a statistician from a third party not involved in the study. This third party was exclusively responsible for randomisation, data management, data analysis, and data quality control
Allocation concealment (selection bias)	Low risk	Supplies of tablets for every participant were identified by a 4-digit number. A sealed envelope containing the randomisation code for each participant was kept by the investigator and was not to be opened during the study, unless a serious life-threatening adverse event occurred
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both NAC and placebo tablets were provided by Hainan Zambon Pharmaceutical Co., Ltd. The placebo was identical in composition, shape, colour, and size but did not contain any active ingredients. NAC and placebo tablets were packaged and labelled in such a way that they could not be distinguished from each other
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All investigators were trained before the trial to ensure reliable study quality, with special emphasis on understanding the protocol, performing spirometry tests, blinding to allocation, managing the drug supply, and maintaining compliance with Good Clinical Practice (GCP). Details of study design were published ahead of the study results
Incomplete outcome data (attrition bias) All outcomes	High risk	24% dropout rate (243/1006); 124/504 (25%) in the intervention group and 119/502 (24%) in the placebo group. Some imbalance noted in the reasons for withdrawal; in the intervention group, more participants withdrew due to adverse events (32 vs 24), whereas in the placebo group, more participants were lost to follow-up (56 vs 48) and withdrew due to lack of efficacy 21 vs 17)
Selective reporting (reporting bias)	Low risk	CONSORT statement was followed to ensure proper reporting of this study

6MWD: six-minute walk distance; ABG: arterial blood gas; ATS: American Thoracic Society; BiPAP: bi-level non-invasive ventilation; BTS: British Thoracic Society; CBSAS: Chronic Bronchitis Symptoms Assessment Scale; CF: cystic fibrosis; COPD: chronic obstructive pulmonary disease; CRQ: Chronic Respiratory Questionnaire; CXR: chest X-ray; ERS: European Respiratory Society; $FEF_{25\%-75\%}$: forced expiratory flow at 25-75% of the pulmonary volume; FEV_1: forced expiratory volume in one second; FOT: forced oscillation technique; FVC: forced vital capacity; GI: gastrointestinal; GOLD: Global Initiative for Obstructive Lung Disease; IC: inspiratory capacity; ICS: inhaled corticosteroids; ITT: intention-to-treat; LTOT: long-term oxygen therapy; LVRS: lung volume reduction surgery; MI: myocardial infarction; MRC: Medical Research Council; NAC: N-acetylcysteine; NYHA: New York Heart Association; OCS: oral corticosteroids; OT: on treatment; $PaCO_2$: partial pressure of carbon dioxide; PaO_2: partial pressure of oxygen; PEFR: peak expiratory flow rate; PKU: phenylketonuria; pMDI: pressurised metered-dose inhaler; PP: per protocol; SABA: short-acting beta-agonist; SCMC-Lys: carbocysteine lysine salt monohydrate; SD: standard deviation; SE: standard error; SF-36: Short Form-36; SGRQ: St. George's Respiratory Questionnaire; TB: tuberculosis ; VC: vital capacity; WHO: World Health Organization.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Baglioni 2001	Preliminary, small, open RCT of NAC vs placebo in patients on LTOT, published in abstract form only, with no numerical data on clinical outcomes
Cattaneo 2001	Only 20 days long
Christensen 1971	No response to 2 letters requesting more data. Old study - unlikely to be successful with further attempts. Did not evaluate primary outcome, although did evaluate days sick
Edwards 1976	Did not evaluate primary outcome
Habich 1994	Included both patients with asthma and patients with COPD
Kasielski 2001	Did not evaluate clinical outcomes
Lukas 2005	Translated from German. Patients with chronic bronchitis given NAC, placebo, Vit C or NAC + Vit C for 3 months. Did not evaluate primary outcome. Outcomes were lung function, symptoms, neutrophils, and other blood outcomes such as oxidising ability. No numerical data presented on lung function or symptoms, although study authors reported no differences for either of these
Maesen 1980	Did not evaluate primary outcome
Michnar 1996	Did not evaluate primary outcome
Moretti 2011	Acute setting; 10 days of treatment with erdosteine
Moretti 2014	Acute setting; 10 days of treatment with erdosteine
Pirabbasi 2016	Four-arm study including NAC and placebo; focus on nutritional and antioxidant status
Rubin 1996	Did not evaluate primary outcome
Saibene 2016	Trial not an RCT. Used a before and after design with all participants taking carbocysteine
Salve 2016	Randomised trial of combined effect of NAC and daily physical activity in stable COPD; thus impossible to determine NAC effect
Sushko 2015	Study specifically in people with COPD post-Chernobyl, so not a typical, stable COPD population
Tatsumi 2007a	Even though randomised, not placebo-controlled
Tatsumi 2007b	Even though randomised, not placebo-controlled
Velazquez 2001	Only 4 weeks long
Wilhelmi 2010	Has been translated from German. Patients with COPD given cineole or placebo for 6 months. Evaluated primary outcome of exacerbations; although P values given for a significant reduction in exacerbations with cineole compared with placebo, no data supplied for event rates. Appears to be a short report summarising original trial

COPD: chronic obstructive pulmonary disease; LTOT: long-term oxygen therapy; NAC: N-acetylcysteine; RCT: randomised controlled trial; vs: versus.

Characteristics of studies awaiting assessment *[ordered by study ID]*

CTRI/2015/01/005432

Methods	Randomised, parallel-group, multiple-arm trial
Participants	Included people with COPD, diagnosed clinically and spirometrically, symptoms of breathlessness, chest tightness and cough with or without sputum, GOLD classification I to III Excluded people with respiratory failure or bronchial asthma; pregnant and lactating mothers; people with clinically relevant, abnormal laboratory values suggesting an unknown disease requiring further investigation; people with psychotic; people with HIV/HBsAg/Anti-HCV-positive serology and immune compromised patients
Interventions	• Standard therapy + oral Superoxide Dismutase (SOD) 1 tab once daily (140 IU) for 12 weeks • Standard therapy + oral N-acetyl-L-cysteine (NAC) 600 mg once daily for 12 weeks • Standard therapy for 12 weeks
Outcomes	Lung function tests, haemogram with ESR, blood sugar, ECG, X-ray chest P/A view, liver function tests, renal function tests
Notes	Study authors contacted 18/12/17, and again 11/01/18, for further information. To date, no response received Contact details: Dr Waseem Rizvi, Associate Professor Department of Pharmacology Jawaharlal Nehru Medical College, AMU Aligarh Tuuar Pradesh 202002 India Email: waseemnakhat@gmail.com

COPD: chronic obstructive pulmonary disease; ECG: electrocardiogram; ESR: erythrocyte sedimentation rate; GOLD: Global Initiative for Obstructive Lung Disease; HBsAg: surface antigen of hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; NAC: N-acetylcysteine; P/A: posteroanterior.

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR-IIR-17012604

Trial name or title	Long-term regular treatment of early COPD with randomised, double-blind, placebo-controlled multi-centre clinical study with acetylcysteine effervescent tablets
Methods	Parallel randomised double-blind placebo-controlled trial
Participants	Aged 40 to 80 years, male or female, community or outpatient; with respiratory symptoms (chronic cough, sputum, shortness of breath) and/or chronic obstructive pulmonary exposure risk factors (smoking, occupational exposure, indoor and outdoor air pollution, family history of COPD, recurrent respiratory tract infection, low birth weight, and genetic factors, etc.); GOLD stage I to II COPD: $FEV_1/FVC < 70\%$; and $FEV_1 \geq 50\%$ predicted after 20 minutes with 400 µg of salbutamol inhalation; patients in a stable period, that is, nearly 4 weeks without COPD acute exacerbations; patient is

ChiCTR-IIR-17012604 *(Continued)*

	able to communicate in words, agrees, and has the ability to complete the test-related auxiliary examination. Signs informed consent
Interventions	Acetylcysteine effervescent tablets vs placebo
Outcomes	Lung function, number of acute exacerbations of COPD, quality of life (CAT), symptom score, COPD acute exacerbation severity, adverse events, attrition
Starting date	2017-09-06
Contact information	Yumin Zhou: zhouyumin410@126.com The First Affiliated Hospital of Guangzhou Medical University 151 Yanjiang Road Guangzhou Guangdong China
Notes	

ChiCTR1800016712

Trial name or title	Early intervention with carbocysteine and low-dose theophylline in Chinese patients with chronic obstructive pulmonary disease
Methods	Multi-centre clinical study screening for effective drugs for early-stage COPD. Parallel RCT
Participants	Community or clinic COPD patients, between 40 and 80 years of age, male or female; FEV_1/FVC < 70% after inhaled bronchodilator; FEV_1 50% predicted (Gold stage I to II); no acute exacerbation of COPD in the last 4 weeks; ability to communicate in languages or words; ability to voluntarily participate in the study and sign informed consent
Interventions	Carbocysteine tablets 500 mg, 3 times daily; theophylline sustained-release tablets 100 mg, 2 times daily; carbocysteine-placebo group: carbocysteine-placebo tablets 500 mg 3 times daily; theophylline-placebo group: theophylline sustained-release placebo tablets 100 mg, 2 times daily
Outcomes	Lung function; number of COPD exacerbations; symptom score; time to first acute exacerbation of COPD; severity, interval, and duration of acute exacerbations of COPD; dropout rate; administration of rescue medication; cost-effectiveness analysis
Starting date	2018-06-25
Contact information	Wang Qiuyue: qywngcmu@163.com The First Hospital of China Medical University 155 Nanjing Street North Heping District Shenyang, Liaoning China +86 13998892756

ChiCTR1800016712 *(Continued)*

Notes

CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; GOLD: Global Initiative for Obstructive Lung Disease; RCT: randomised controlled trial.

DATA AND ANALYSES

Comparison 1. Mucolytic versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with no exacerbations in study period	28	6723	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.73 [1.56, 1.91]
1.1 Double-blind	26	6460	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.69 [1.53, 1.88]
1.2 Single-blind/open	2	263	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.91 [1.76, 4.83]
2 Participants with no exacerbation by decade, double-blind trials only	26	6460	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.69 [1.53, 1.88]
2.1 Before 1990	12	2304	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.34 [1.97, 2.79]
2.2 1990 to 1999	5	1105	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.91 [1.50, 2.44]
2.3 2000 to 2009	5	1477	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.24 [1.01, 1.54]
2.4 2010 onwards	4	1574	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.28 [1.03, 1.59]
3 Participants with no exacerbations in the study period - winter treatment only	21	4007	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.20 [1.93, 2.51]
3.1 Double-blind	20	3844	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.18 [1.91, 2.49]
3.2 Single-blind/open	1	163	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.85 [1.49, 5.46]
4 Participants with no exacerbations in study period - by dose or type of mucolytic	28	6723	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.73 [1.56, 1.91]
4.1 NAC 400 mg	3	717	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.98 [2.21, 4.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 NAC 600 mg	9	1425	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.76 [1.40, 2.21]
4.3 NAC 1200 mg	3	1213	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.95, 1.57]
4.5 NAC 3200 mg	1	45	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.52 [0.14, 2.01]
4.6 Carbocysteine	4	1251	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.41 [1.13, 1.77]
4.7 Other mucolytic	8	2072	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.97 [1.64, 2.36]
5 Participants with no exacerbations in study period - by FEV_1	28	6723	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.73 [1.56, 1.91]
5.1 Mean FEV_1 > 50% predicted	24	5352	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.81 [1.62, 2.03]
5.2 Mean FEV_1 ≤ 50% predicted	4	1371	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.38 [1.08, 1.75]
6 Participants with no exacerbations in study period - by study duration	28	6723	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.73 [1.56, 1.91]
6.1 Duration ≤ 3 months	5	903	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.14 [1.62, 2.82]
6.2 Duration > 3 months and < 12 months	18	3278	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.20 [1.91, 2.54]
6.3 Duration ≥ 12 months	5	2542	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.98, 1.37]
7 Participants with no exacerbations in study period - by country	28	6723	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.73 [1.56, 1.91]
7.1 Italian	11	2407	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.44 [2.06, 2.88]
7.2 Rest of world	17	4316	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.41 [1.25, 1.61]
8 Participants with no exacerbations in study period - by history of exacerbation	28	6723	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.73 [1.56, 1.91]
8.1 Exacerbation history requirement for inclusion	16	4192	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.50 [1.32, 1.70]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.2 Exacerbation history not a requirement for inclusion	12	2531	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.18 [1.85, 2.57]
9 Participants with no exacerbations in study period - by ICS use	28	6723	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.73 [1.56, 1.91]
9.1 ICS allowed	15	4401	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.65 [1.46, 1.87]
9.2 ICS not allowed	6	1431	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.85 [1.49, 2.31]
9.3 ICS unclear	7	891	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.95 [1.48, 2.58]
10 Number of exacerbations per participant per month			Other data	No numeric data
11 Days of disability per participant per month	9	2259	Mean Difference (IV, Fixed, 95% CI)	-0.43 [-0.56, -0.30]
12 Days on antibiotics per participant per month	3	714	Mean Difference (IV, Fixed, 95% CI)	-0.53 [-0.76, -0.31]
13 FEV_1 at end of study	14	3473	Mean Difference (IV, Fixed, 95% CI)	0.04 [0.01, 0.07]
13.1 Double-blind	13	3310	Mean Difference (IV, Fixed, 95% CI)	0.04 [0.01, 0.07]
13.2 Single-blind	1	163	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.10, 0.26]
14 Percent predicted FEV_1	4	414	Mean Difference (IV, Fixed, 95% CI)	4.79 [1.97, 7.62]
14.1 Double-blind	2	230	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-4.72, 4.47]
14.2 Single-blind	1	100	Mean Difference (IV, Fixed, 95% CI)	0.70 [-4.02, 5.42]
14.3 No blinding	1	84	Mean Difference (IV, Fixed, 95% CI)	17.31 [11.83, 22.79]
15 PEFR at end of study	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
15.1 Double-blind	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 FVC at end of study	12	3127	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.00, 0.10]
17 Adverse effects	24	7264	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.74, 0.94]
18 Hospitalisation during study period	5	1833	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.68 [0.52, 0.89]
19 Death during study period	11	3527	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.51, 1.87]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20 Health-related quality of life (total score St. George's Respiratory Questionnaire)	7	2721	Mean Difference (IV, Fixed, 95% CI)	-1.37 [-2.85, 0.11]
21 Health-related quality of life (total score COPD Assessment Test)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 Mucolytic versus placebo, Outcome 1 Participants with no exacerbations in study period.

Study or subgroup	Mucolytic n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.1.1 Double-blind					
Allegra 1996	111/171	89/181		5.74%	1.9[1.24,2.89]
Babolini 1980	134/254	58/241		7.81%	3.34[2.33,4.79]
Boman 1983	46/98	29/105		3.15%	2.28[1.29,4.03]
Borgia 1981	7/10	4/9		0.32%	2.7[0.46,15.93]
Castiglioni 1986	240/311	179/302		8.81%	2.28[1.63,3.21]
Cremonini 1986	8/21	0/20		0.44%	10.66[2.32,49.05]
Dal Negro 2017	91/215	70/230		6.83%	1.67[1.14,2.46]
Grassi 1976	18/35	11/34		1.13%	2.16[0.84,5.59]
Grassi 1994	25/42	14/41		1.39%	2.74[1.16,6.45]
Grillage 1985	35/54	29/55		1.77%	1.64[0.77,3.5]
Hansen 1994	36/59	34/70		2.13%	1.64[0.82,3.29]
Jackson 1984	41/61	36/60		1.87%	1.36[0.65,2.85]
Johnson 2016	16/23	18/22		0.56%	0.52[0.14,2.01]
Malerba 2004	64/115	63/119		3.87%	1.11[0.67,1.86]
McGavin 1985	11/72	8/76		1.11%	1.52[0.58,3.98]
Meister 1986	37/90	34/91		2.88%	1.17[0.64,2.12]
Meister 1999	79/122	56/124		4.06%	2.2[1.33,3.63]
Moretti 2004	26/63	13/61		1.79%	2.5[1.18,5.33]
Nowak 1999	114/147	101/148		3.88%	1.6[0.96,2.67]
Olivieri 1987	56/110	21/104		3.28%	3.77[2.16,6.58]
Rasmussen 1988	28/44	24/47		1.49%	1.66[0.73,3.8]
Schermer 2009	22/96	27/96		2.43%	0.76[0.4,1.45]
Tse 2013	28/58	21/62		1.94%	1.81[0.87,3.73]
Worth 2009	79/110	60/110		3.41%	2.09[1.21,3.62]
Zheng 2008	159/353	151/354		11.57%	1.1[0.82,1.48]
Zheng 2014	130/482	122/482		12.36%	1.09[0.82,1.45]
Subtotal (95% CI)	**3216**	**3244**		**96.03%**	**1.69[1.53,1.88]**
Total events: 1641 (Mucolytic), 1272 (Control)					
Heterogeneity: Tau^2=0; Chi^2=66.19, df=25(P<0.0001); I^2=62.23%					
Test for overall effect: Z=10.01(P<0.0001)					
1.1.2 Single-blind/open					
Bachh 2007	25/50	12/50		1.56%	3.02[1.35,6.77]
Pela 1999	37/83	17/80		2.41%	2.85[1.49,5.46]
Subtotal (95% CI)	**133**	**130**		**3.97%**	**2.91[1.76,4.83]**

Favours control — Favours mucolytic

Study or subgroup	Mucolytic n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Total events: 62 (Mucolytic), 29 (Control)					
Heterogeneity: Tau²=0; Chi²=0.01, df=1(P=0.91); I²=0%					
Test for overall effect: Z=4.14(P<0.0001)					
Total (95% CI)	**3349**	**3374**		**100%**	**1.73[1.56,1.91]**
Total events: 1703 (Mucolytic), 1301 (Control)					
Heterogeneity: Tau²=0; Chi²=70.43, df=27(P<0.0001); I²=61.67%					
Test for overall effect: Z=10.64(P<0.0001)					
Test for subgroup differences: Chi²=4.23, df=1 (P=0.04), I²=76.39%					

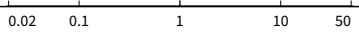
Favours control 0.005 0.1 1 10 200 Favours mucolytic

Analysis 1.2. Comparison 1 Mucolytic versus placebo, Outcome 2 Participants with no exacerbation by decade, double-blind trials only.

Study or subgroup	Mucolytic n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.2.1 Before 1990					
Grassi 1976	18/35	11/34		1.18%	2.16[0.84,5.59]
Babolini 1980	134/254	58/241		8.13%	3.34[2.33,4.79]
Borgia 1981	7/10	4/9		0.34%	2.7[0.46,15.93]
Boman 1983	46/98	29/105		3.28%	2.28[1.29,4.03]
Jackson 1984	41/61	36/60		1.95%	1.36[0.65,2.85]
McGavin 1985	11/72	8/76		1.15%	1.52[0.58,3.98]
Grillage 1985	35/54	29/55		1.84%	1.64[0.77,3.5]
Meister 1986	37/90	34/91		3%	1.17[0.64,2.12]
Cremonini 1986	8/21	0/20		0.46%	10.66[2.32,49.05]
Castiglioni 1986	240/311	179/302		9.18%	2.28[1.63,3.21]
Olivieri 1987	56/110	21/104		3.42%	3.77[2.16,6.58]
Rasmussen 1988	28/44	24/47		1.56%	1.66[0.73,3.8]
Subtotal (95% CI)	**1160**	**1144**		**35.48%**	**2.34[1.97,2.79]**
Total events: 661 (Mucolytic), 433 (Control)					
Heterogeneity: Tau²=0; Chi²=19.97, df=11(P=0.05); I²=44.9%					
Test for overall effect: Z=9.65(P<0.0001)					
1.2.2 1990 to 1999					
Grassi 1994	25/42	14/41		1.45%	2.74[1.16,6.45]
Hansen 1994	36/59	34/70		2.21%	1.64[0.82,3.29]
Allegra 1996	111/171	89/181		5.98%	1.9[1.24,2.89]
Nowak 1999	114/147	101/148		4.04%	1.6[0.96,2.67]
Meister 1999	79/122	56/124		4.23%	2.2[1.33,3.63]
Subtotal (95% CI)	**541**	**564**		**17.91%**	**1.91[1.5,2.44]**
Total events: 365 (Mucolytic), 294 (Control)					
Heterogeneity: Tau²=0; Chi²=1.62, df=4(P=0.8); I²=0%					
Test for overall effect: Z=5.22(P<0.0001)					
1.2.3 2000 to 2009					
Moretti 2004	26/63	13/61		1.86%	2.5[1.18,5.33]
Malerba 2004	64/115	63/119		4.03%	1.11[0.67,1.86]
Zheng 2008	159/353	151/354		12.05%	1.1[0.82,1.48]

Favours control 0.02 0.1 1 10 50 Favours mucolytic

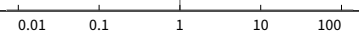
Study or subgroup	Mucolytic n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Worth 2009	79/110	60/110		3.55%	2.09[1.21,3.62]
Schermer 2009	22/96	27/96		2.54%	0.76[0.4,1.45]
Subtotal (95% CI)	**737**	**740**		**24.02%**	**1.24[1.01,1.54]**
Total events: 350 (Mucolytic), 314 (Control)					
Heterogeneity: Tau^2=0; Chi^2=9.82, df=4(P=0.04); I^2=59.25%					
Test for overall effect: Z=2.04(P=0.04)					
1.2.4 2010 onwards					
Tse 2013	28/58	21/62		2.02%	1.81[0.87,3.73]
Zheng 2014	130/482	122/482		12.88%	1.09[0.82,1.45]
Johnson 2016	16/23	18/22		0.59%	0.52[0.14,2.01]
Dal Negro 2017	91/215	70/230		7.11%	1.67[1.14,2.46]
Subtotal (95% CI)	**778**	**796**		**22.59%**	**1.28[1.03,1.59]**
Total events: 265 (Mucolytic), 231 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.61, df=3(P=0.13); I^2=46.52%					
Test for overall effect: Z=2.23(P=0.03)					
Total (95% CI)	**3216**	**3244**		**100%**	**1.69[1.53,1.88]**
Total events: 1641 (Mucolytic), 1272 (Control)					
Heterogeneity: Tau^2=0; Chi^2=66.19, df=25(P<0.0001); I^2=62.23%					
Test for overall effect: Z=10.01(P<0.0001)					
Test for subgroup differences: Chi^2=29.17, df=1 (P<0.0001), I^2=89.72%					



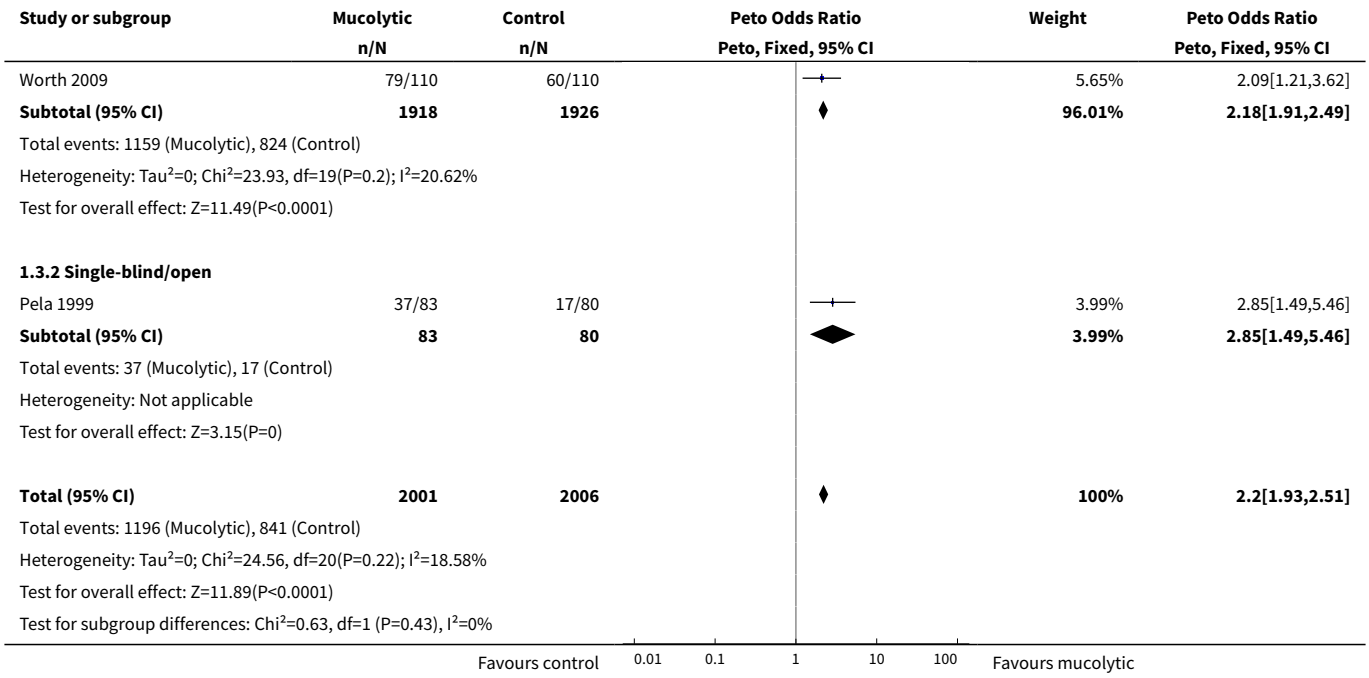
Favours control — Favours mucolytic

Analysis 1.3. Comparison 1 Mucolytic versus placebo, Outcome 3 Participants with no exacerbations in the study period - winter treatment only.

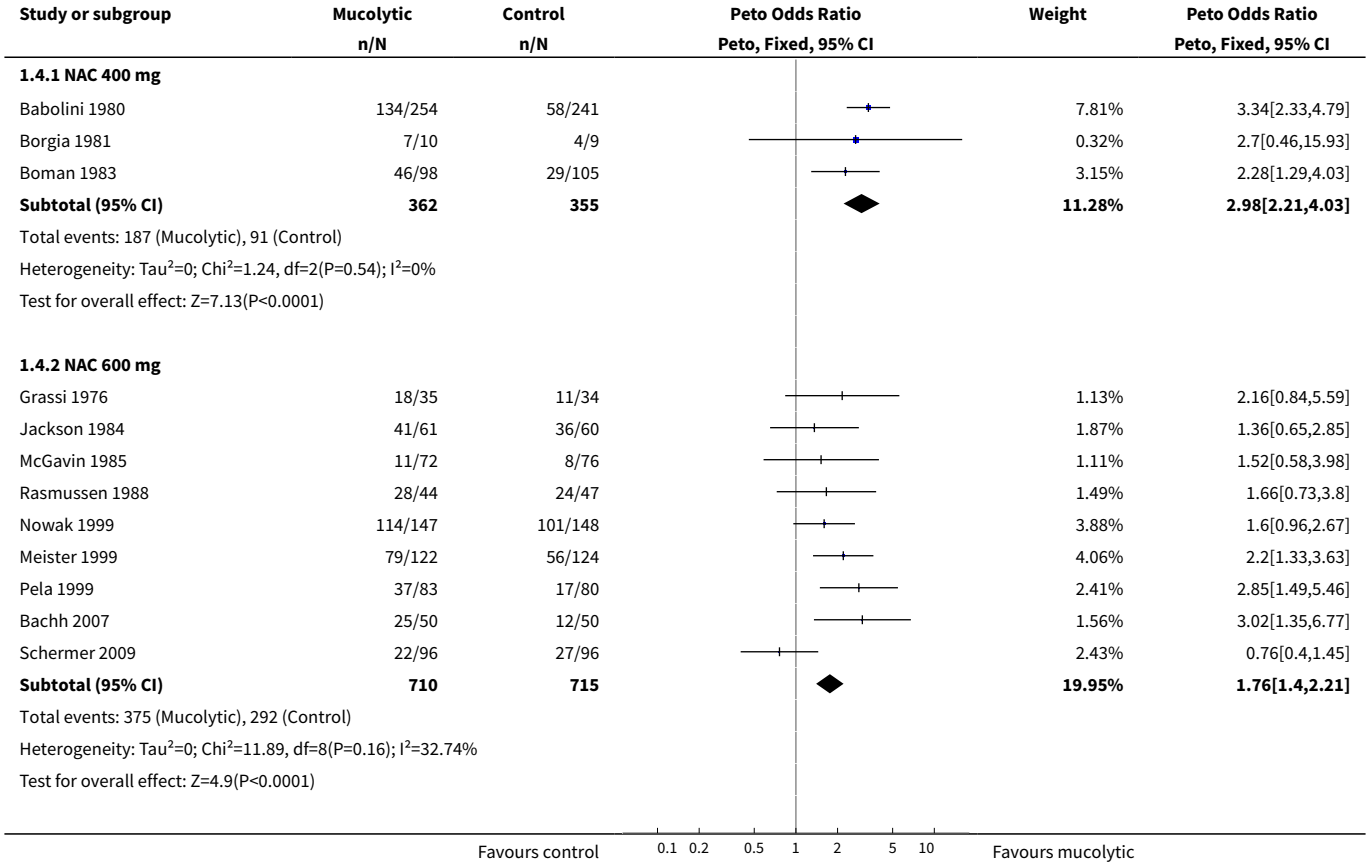
Study or subgroup	Mucolytic n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.3.1 Double-blind					
Allegra 1996	111/171	89/181		9.51%	1.9[1.24,2.89]
Babolini 1980	134/254	58/241		12.94%	3.34[2.33,4.79]
Boman 1983	46/98	29/105		5.22%	2.28[1.29,4.03]
Borgia 1981	7/10	4/9		0.54%	2.7[0.46,15.93]
Castiglioni 1986	240/311	179/302		14.6%	2.28[1.63,3.21]
Cremonini 1986	8/21	0/20		0.73%	10.66[2.32,49.05]
Grassi 1976	18/35	11/34		1.87%	2.16[0.84,5.59]
Grassi 1994	25/42	14/41		2.3%	2.74[1.16,6.45]
Grillage 1985	35/54	29/55		2.93%	1.64[0.77,3.5]
Hansen 1994	36/59	34/70		3.52%	1.64[0.82,3.29]
Jackson 1984	41/61	36/60		3.1%	1.36[0.65,2.85]
Malerba 2004	28/44	24/47		2.47%	1.66[0.73,3.8]
McGavin 1985	11/72	8/76		1.83%	1.52[0.58,3.98]
Meister 1986	37/90	34/91		4.77%	1.17[0.64,2.12]
Meister 1999	79/122	56/124		6.72%	2.2[1.33,3.63]
Moretti 2004	26/63	13/61		2.96%	2.5[1.18,5.33]
Nowak 1999	114/147	101/148		6.43%	1.6[0.96,2.67]
Olivieri 1987	56/110	21/104		5.44%	3.77[2.16,6.58]
Rasmussen 1988	28/44	24/47		2.47%	1.66[0.73,3.8]

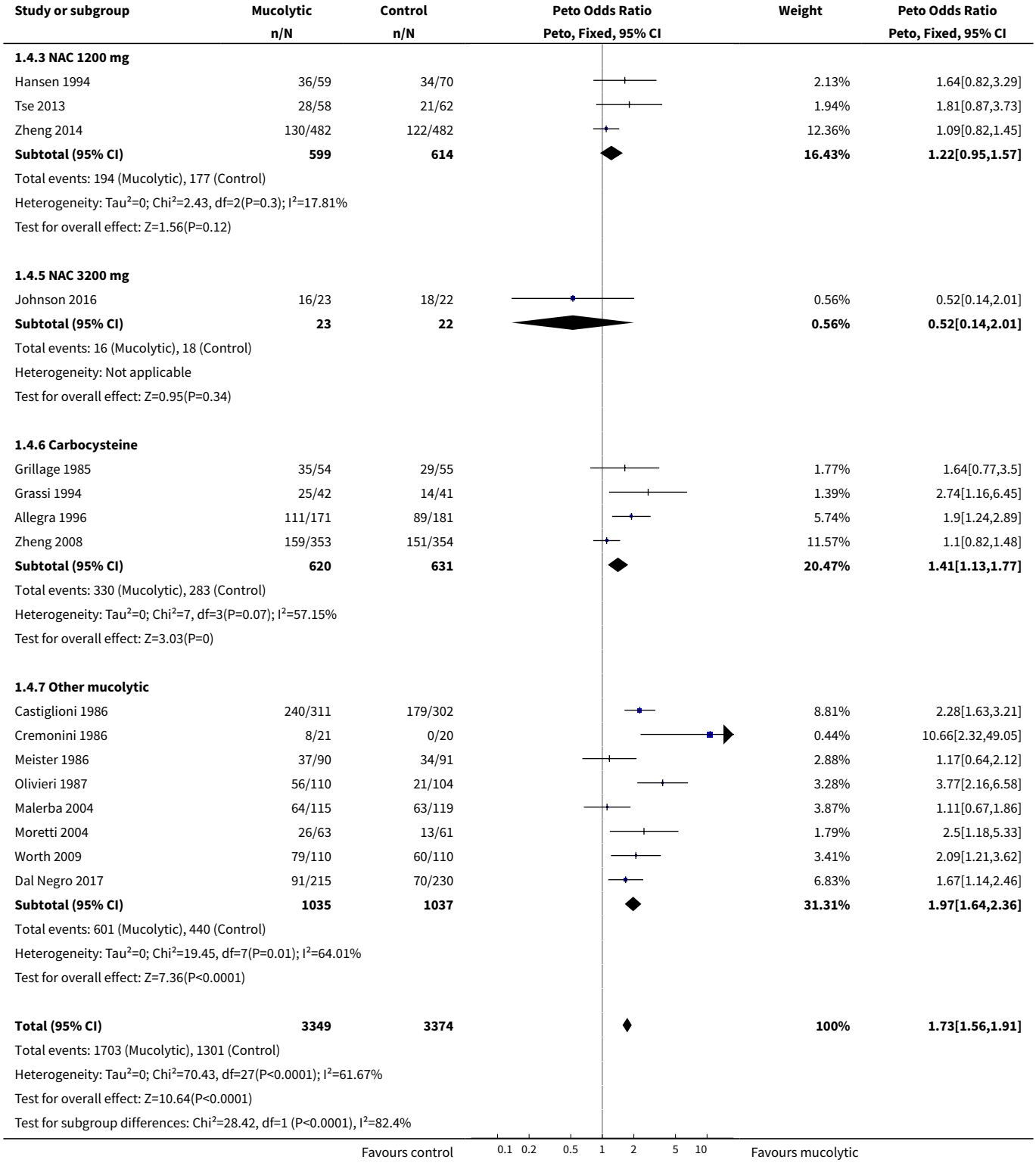


Favours control — Favours mucolytic



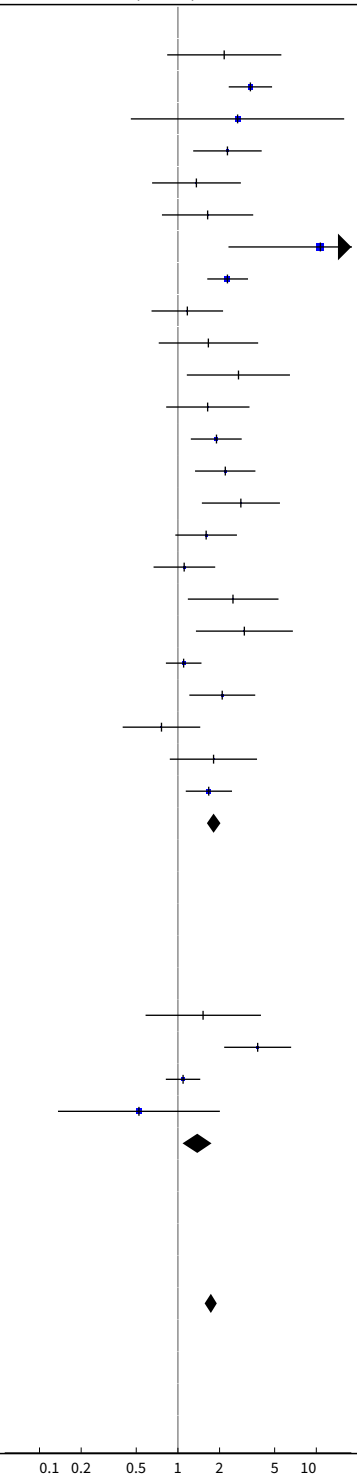
Analysis 1.4. Comparison 1 Mucolytic versus placebo, Outcome 4 Participants with no exacerbations in study period - by dose or type of mucolytic.





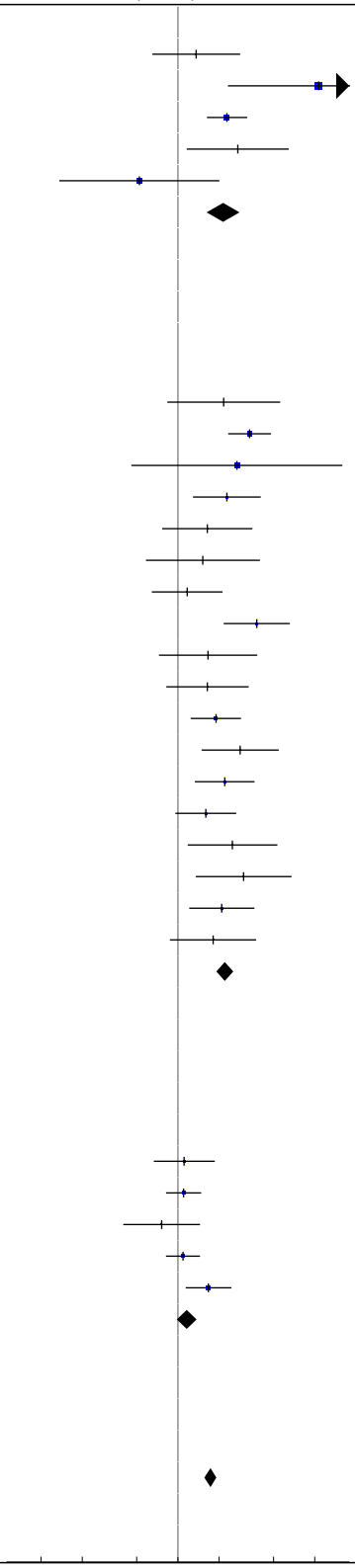
Analysis 1.5. Comparison 1 Mucolytic versus placebo, Outcome 5 Participants with no exacerbations in study period - by FEV_1.

Study or subgroup	Mucolytic n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.5.1 Mean FEV_1 > 50% predicted					
Grassi 1976	18/35	11/34		1.13%	2.16[0.84,5.59]
Babolini 1980	134/254	58/241		7.81%	3.34[2.33,4.79]
Borgia 1981	7/10	4/9		0.32%	2.7[0.46,15.93]
Boman 1983	46/98	29/105		3.15%	2.28[1.29,4.03]
Jackson 1984	41/61	36/60		1.87%	1.36[0.65,2.85]
Grillage 1985	35/54	29/55		1.77%	1.64[0.77,3.5]
Cremonini 1986	8/21	0/20		0.44%	10.66[2.32,49.05]
Castiglioni 1986	240/311	179/302		8.81%	2.28[1.63,3.21]
Meister 1986	37/90	34/91		2.88%	1.17[0.64,2.12]
Rasmussen 1988	28/44	24/47		1.49%	1.66[0.73,3.8]
Grassi 1994	25/42	14/41		1.39%	2.74[1.16,6.45]
Hansen 1994	36/59	34/70		2.13%	1.64[0.82,3.29]
Allegra 1996	111/171	89/181		5.74%	1.9[1.24,2.89]
Meister 1999	79/122	56/124		4.06%	2.2[1.33,3.63]
Pela 1999	37/83	17/80		2.41%	2.85[1.49,5.46]
Nowak 1999	114/147	101/148		3.88%	1.6[0.96,2.67]
Malerba 2004	64/115	63/119		3.87%	1.11[0.67,1.86]
Moretti 2004	26/63	13/61		1.79%	2.5[1.18,5.33]
Bachh 2007	25/50	12/50		1.56%	3.02[1.35,6.77]
Zheng 2008	159/353	151/354		11.57%	1.1[0.82,1.48]
Worth 2009	79/110	60/110		3.41%	2.09[1.21,3.62]
Schermer 2009	22/96	27/96		2.43%	0.76[0.4,1.45]
Tse 2013	28/58	21/62		1.94%	1.81[0.87,3.73]
Dal Negro 2017	91/215	70/230		6.83%	1.67[1.14,2.46]
Subtotal (95% CI)	**2662**	**2690**		**82.68%**	**1.81[1.62,2.03]**
Total events: 1490 (Mucolytic), 1132 (Control)					
Heterogeneity: Tau^2=0; Chi^2=49.15, df=23(P=0); I^2=53.2%					
Test for overall effect: Z=10.52(P<0.0001)					
1.5.2 Mean FEV_1 ≤ 50% predicted					
McGavin 1985	11/72	8/76		1.11%	1.52[0.58,3.98]
Olivieri 1987	56/110	21/104		3.28%	3.77[2.16,6.58]
Zheng 2014	130/482	122/482		12.36%	1.09[0.82,1.45]
Johnson 2016	16/23	18/22		0.56%	0.52[0.14,2.01]
Subtotal (95% CI)	**687**	**684**		**17.32%**	**1.38[1.08,1.75]**
Total events: 213 (Mucolytic), 169 (Control)					
Heterogeneity: Tau^2=0; Chi^2=17.14, df=3(P=0); I^2=82.5%					
Test for overall effect: Z=2.58(P=0.01)					
Total (95% CI)	**3349**	**3374**		**100%**	**1.73[1.56,1.91]**
Total events: 1703 (Mucolytic), 1301 (Control)					
Heterogeneity: Tau^2=0; Chi^2=70.43, df=27(P<0.0001); I^2=61.67%					
Test for overall effect: Z=10.64(P<0.0001)					
Test for subgroup differences: Chi^2=4.14, df=1 (P=0.04), I^2=75.87%					

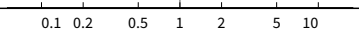


Analysis 1.6. Comparison 1 Mucolytic versus placebo, Outcome 6 Participants with no exacerbations in study period - by study duration.

Study or subgroup	Mucolytic n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.6.1 Duration ≤ 3 months					
Jackson 1984	41/61	36/60		1.87%	1.36[0.65,2.85]
Cremonini 1986	8/21	0/20		0.44%	10.66[2.32,49.05]
Castiglioni 1986	240/311	179/302		8.81%	2.28[1.63,3.21]
Grassi 1994	25/42	14/41		1.39%	2.74[1.16,6.45]
Johnson 2016	16/23	18/22		0.56%	0.52[0.14,2.01]
Subtotal (95% CI)	**458**	**445**		**13.08%**	**2.14[1.62,2.82]**
Total events: 330 (Mucolytic), 247 (Control)					
Heterogeneity: Tau²=0; Chi²=10.37, df=4(P=0.03); I²=61.42%					
Test for overall effect: Z=5.33(P<0.0001)					
1.6.2 Duration > 3 months and < 12 months					
Grassi 1976	18/35	11/34		1.13%	2.16[0.84,5.59]
Babolini 1980	134/254	58/241		7.81%	3.34[2.33,4.79]
Borgia 1981	7/10	4/9		0.32%	2.7[0.46,15.93]
Boman 1983	46/98	29/105		3.15%	2.28[1.29,4.03]
Grillage 1985	35/54	29/55		1.77%	1.64[0.77,3.5]
McGavin 1985	11/72	8/76		1.11%	1.52[0.58,3.98]
Meister 1986	37/90	34/91		2.88%	1.17[0.64,2.12]
Olivieri 1987	56/110	21/104		3.28%	3.77[2.16,6.58]
Rasmussen 1988	28/44	24/47		1.49%	1.66[0.73,3.8]
Hansen 1994	36/59	34/70		2.13%	1.64[0.82,3.29]
Allegra 1996	111/171	89/181		5.74%	1.9[1.24,2.89]
Pela 1999	37/83	17/80		2.41%	2.85[1.49,5.46]
Meister 1999	79/122	56/124		4.06%	2.2[1.33,3.63]
Nowak 1999	114/147	101/148		3.88%	1.6[0.96,2.67]
Moretti 2004	26/63	13/61		1.79%	2.5[1.18,5.33]
Bachh 2007	25/50	12/50		1.56%	3.02[1.35,6.77]
Worth 2009	79/110	60/110		3.41%	2.09[1.21,3.62]
Tse 2013	28/58	21/62		1.94%	1.81[0.87,3.73]
Subtotal (95% CI)	**1630**	**1648**		**49.86%**	**2.2[1.91,2.54]**
Total events: 907 (Mucolytic), 621 (Control)					
Heterogeneity: Tau²=0; Chi²=18.97, df=17(P=0.33); I²=10.37%					
Test for overall effect: Z=10.84(P<0.0001)					
1.6.3 Duration ≥ 12 months					
Malerba 2004	64/115	63/119		3.87%	1.11[0.67,1.86]
Zheng 2008	159/353	151/354		11.57%	1.1[0.82,1.48]
Schermer 2009	22/96	27/96		2.43%	0.76[0.4,1.45]
Zheng 2014	130/482	122/482		12.36%	1.09[0.82,1.45]
Dal Negro 2017	91/215	70/230		6.83%	1.67[1.14,2.46]
Subtotal (95% CI)	**1261**	**1281**		**37.06%**	**1.16[0.98,1.37]**
Total events: 466 (Mucolytic), 433 (Control)					
Heterogeneity: Tau²=0; Chi²=5.38, df=4(P=0.25); I²=25.65%					
Test for overall effect: Z=1.74(P=0.08)					
Total (95% CI)	**3349**	**3374**		**100%**	**1.73[1.56,1.91]**
Total events: 1703 (Mucolytic), 1301 (Control)					
Heterogeneity: Tau²=0; Chi²=70.43, df=27(P<0.0001); I²=61.67%					



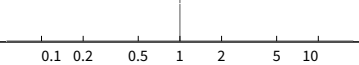
Study or subgroup	Mucolytic n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Test for overall effect: Z=10.64(P<0.0001)					
Test for subgroup differences: Chi²=35.72, df=1 (P<0.0001), I²=94.4%					



Favours control — Favours mucolytic

Analysis 1.7. Comparison 1 Mucolytic versus placebo, Outcome 7 Participants with no exacerbations in study period - by country.

Study or subgroup	Mucolytic n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.7.1 Italian					
Grassi 1976	18/35	11/34		1.13%	2.16[0.84,5.59]
Babolini 1980	134/254	58/241		7.81%	3.34[2.33,4.79]
Borgia 1981	7/10	4/9		0.32%	2.7[0.46,15.93]
Castiglioni 1986	240/311	179/302		8.81%	2.28[1.63,3.21]
Cremonini 1986	8/21	0/20		0.44%	10.66[2.32,49.05]
Olivieri 1987	56/110	21/104		3.28%	3.77[2.16,6.58]
Grassi 1994	25/42	14/41		1.39%	2.74[1.16,6.45]
Allegra 1996	111/171	89/181		5.74%	1.9[1.24,2.89]
Pela 1999	37/83	17/80		2.41%	2.85[1.49,5.46]
Malerba 2004	64/115	63/119		3.87%	1.11[0.67,1.86]
Moretti 2004	26/63	13/61		1.79%	2.5[1.18,5.33]
Subtotal (95% CI)	**1215**	**1192**		**37%**	**2.44[2.06,2.88]**
Total events: 726 (Mucolytic), 469 (Control)					
Heterogeneity: Tau²=0; Chi²=19.65, df=10(P=0.03); I²=49.12%					
Test for overall effect: Z=10.51(P<0.0001)					
1.7.2 Rest of world					
Boman 1983	46/98	29/105		3.15%	2.28[1.29,4.03]
Jackson 1984	41/61	36/60		1.87%	1.36[0.65,2.85]
McGavin 1985	11/72	8/76		1.11%	1.52[0.58,3.98]
Grillage 1985	35/54	29/55		1.77%	1.64[0.77,3.5]
Meister 1986	37/90	34/91		2.88%	1.17[0.64,2.12]
Rasmussen 1988	28/44	24/47		1.49%	1.66[0.73,3.8]
Hansen 1994	36/59	34/70		2.13%	1.64[0.82,3.29]
Meister 1999	79/122	56/124		4.06%	2.2[1.33,3.63]
Nowak 1999	114/147	101/148		3.88%	1.6[0.96,2.67]
Bachh 2007	25/50	12/50		1.56%	3.02[1.35,6.77]
Zheng 2008	159/353	151/354		11.57%	1.1[0.82,1.48]
Schermer 2009	22/96	27/96		2.43%	0.76[0.4,1.45]
Worth 2009	79/110	60/110		3.41%	2.09[1.21,3.62]
Tse 2013	28/58	21/62		1.94%	1.81[0.87,3.73]
Zheng 2014	130/482	122/482		12.36%	1.09[0.82,1.45]
Johnson 2016	16/23	18/22		0.56%	0.52[0.14,2.01]
Dal Negro 2017	91/215	70/230		6.83%	1.67[1.14,2.46]
Subtotal (95% CI)	**2134**	**2182**		**63%**	**1.41[1.25,1.61]**
Total events: 977 (Mucolytic), 832 (Control)					
Heterogeneity: Tau²=0; Chi²=24.84, df=16(P=0.07); I²=35.59%					
Test for overall effect: Z=5.34(P<0.0001)					



Favours control — Favours mucolytic

Study or subgroup	Mucolytic n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Total (95% CI)	**3349**	**3374**		**100%**	**1.73[1.56,1.91]**
Total events: 1703 (Mucolytic), 1301 (Control)					
Heterogeneity: Tau²=0; Chi²=70.43, df=27(P<0.0001); I²=61.67%					
Test for overall effect: Z=10.64(P<0.0001)					
Test for subgroup differences: Chi²=25.94, df=1 (P<0.0001), I²=96.14%					

Favours control 0.1 0.2 0.5 1 2 5 10 Favours mucolytic

Analysis 1.8. Comparison 1 Mucolytic versus placebo, Outcome 8 Participants with no exacerbations in study period - by history of exacerbation.

Study or subgroup	Mucolytic n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.8.1 Exacerbation history requirement for inclusion					
Borgia 1981	7/10	4/9		0.32%	2.7[0.46,15.93]
Boman 1983	46/98	29/105		3.15%	2.28[1.29,4.03]
McGavin 1985	11/72	8/76		1.11%	1.52[0.58,3.98]
Grillage 1985	35/54	29/55		1.77%	1.64[0.77,3.5]
Meister 1986	37/90	34/91		2.88%	1.17[0.64,2.12]
Olivieri 1987	56/110	21/104		3.28%	3.77[2.16,6.58]
Rasmussen 1988	28/44	24/47		1.49%	1.66[0.73,3.8]
Grassi 1994	25/42	14/41		1.39%	2.74[1.16,6.45]
Hansen 1994	36/59	34/70		2.13%	1.64[0.82,3.29]
Nowak 1999	114/147	101/148		3.88%	1.6[0.96,2.67]
Meister 1999	79/122	56/124		4.06%	2.2[1.33,3.63]
Malerba 2004	64/115	63/119		3.87%	1.11[0.67,1.86]
Moretti 2004	26/63	13/61		1.79%	2.5[1.18,5.33]
Zheng 2008	159/353	151/354		11.57%	1.1[0.82,1.48]
Zheng 2014	130/482	122/482		12.36%	1.09[0.82,1.45]
Dal Negro 2017	91/215	70/230		6.83%	1.67[1.14,2.46]
Subtotal (95% CI)	**2076**	**2116**		**61.87%**	**1.5[1.32,1.7]**
Total events: 944 (Mucolytic), 773 (Control)					
Heterogeneity: Tau²=0; Chi²=30.33, df=15(P=0.01); I²=50.54%					
Test for overall effect: Z=6.18(P<0.0001)					
1.8.2 Exacerbation history not a requirement for inclusion					
Grassi 1976	18/35	11/34		1.13%	2.16[0.84,5.59]
Babolini 1980	134/254	58/241		7.81%	3.34[2.33,4.79]
Jackson 1984	41/61	36/60		1.87%	1.36[0.65,2.85]
Cremonini 1986	8/21	0/20		0.44%	10.66[2.32,49.05]
Castiglioni 1986	240/311	179/302		8.81%	2.28[1.63,3.21]
Allegra 1996	111/171	89/181		5.74%	1.9[1.24,2.89]
Pela 1999	37/83	17/80		2.41%	2.85[1.49,5.46]
Bachh 2007	25/50	12/50		1.56%	3.02[1.35,6.77]
Worth 2009	79/110	60/110		3.41%	2.09[1.21,3.62]
Schermer 2009	22/96	27/96		2.43%	0.76[0.4,1.45]
Tse 2013	28/58	21/62		1.94%	1.81[0.87,3.73]
Johnson 2016	16/23	18/22		0.56%	0.52[0.14,2.01]
Subtotal (95% CI)	**1273**	**1258**		**38.13%**	**2.18[1.85,2.57]**
Total events: 759 (Mucolytic), 528 (Control)					

Favours control 0.1 0.2 0.5 1 2 5 10 Favours mucolytic

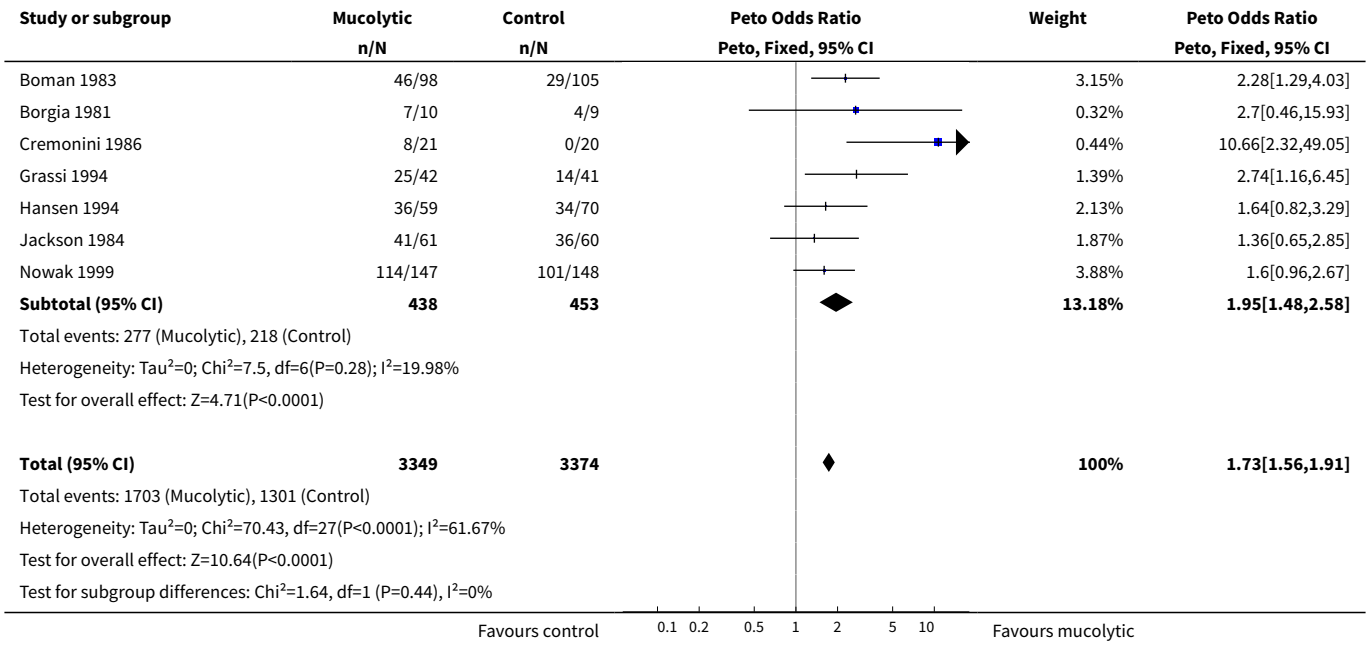
Study or subgroup	Mucolytic n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=27.59, df=11(P=0); I²=60.13%					
Test for overall effect: Z=9.35(P<0.0001)					
Total (95% CI)	**3349**	**3374**		**100%**	**1.73[1.56,1.91]**
Total events: 1703 (Mucolytic), 1301 (Control)					
Heterogeneity: Tau²=0; Chi²=70.43, df=27(P<0.0001); I²=61.67%					
Test for overall effect: Z=10.64(P<0.0001)					
Test for subgroup differences: Chi²=12.51, df=1 (P=0), I²=92.01%					

Favours control 0.1 0.2 0.5 1 2 5 10 Favours mucolytic

Analysis 1.9. Comparison 1 Mucolytic versus placebo, Outcome 9 Participants with no exacerbations in study period - by ICS use.

Study or subgroup	Mucolytic n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.9.1 ICS allowed					
Allegra 1996	111/171	89/181		5.74%	1.9[1.24,2.89]
Babolini 1980	134/254	58/241		7.81%	3.34[2.33,4.79]
Bachh 2007	25/50	12/50		1.56%	3.02[1.35,6.77]
Dal Negro 2017	91/215	70/230		6.83%	1.67[1.14,2.46]
Johnson 2016	16/23	18/22		0.56%	0.52[0.14,2.01]
McGavin 1985	11/72	8/76		1.11%	1.52[0.58,3.98]
Meister 1986	37/90	34/91		2.88%	1.17[0.64,2.12]
Meister 1999	79/122	56/124		4.06%	2.2[1.33,3.63]
Moretti 2004	26/63	13/61		1.79%	2.5[1.18,5.33]
Pela 1999	37/83	17/80		2.41%	2.85[1.49,5.46]
Rasmussen 1988	28/44	24/47		1.49%	1.66[0.73,3.8]
Tse 2013	28/58	21/62		1.94%	1.81[0.87,3.73]
Worth 2009	79/110	60/110		3.41%	2.09[1.21,3.62]
Zheng 2008	159/353	151/354		11.57%	1.1[0.82,1.48]
Zheng 2014	130/482	122/482		12.36%	1.09[0.82,1.45]
Subtotal (95% CI)	**2190**	**2211**		**65.52%**	**1.65[1.46,1.87]**
Total events: 991 (Mucolytic), 753 (Control)					
Heterogeneity: Tau²=0; Chi²=42.37, df=14(P=0); I²=66.96%					
Test for overall effect: Z=7.88(P<0.0001)					
1.9.2 ICS not allowed					
Castiglioni 1986	240/311	179/302		8.81%	2.28[1.63,3.21]
Grassi 1976	18/35	11/34		1.13%	2.16[0.84,5.59]
Grillage 1985	35/54	29/55		1.77%	1.64[0.77,3.5]
Malerba 2004	64/115	63/119		3.87%	1.11[0.67,1.86]
Olivieri 1987	56/110	21/104		3.28%	3.77[2.16,6.58]
Schermer 2009	22/96	27/96		2.43%	0.76[0.4,1.45]
Subtotal (95% CI)	**721**	**710**		**21.3%**	**1.85[1.49,2.31]**
Total events: 435 (Mucolytic), 330 (Control)					
Heterogeneity: Tau²=0; Chi²=18.92, df=5(P=0); I²=73.57%					
Test for overall effect: Z=5.53(P<0.0001)					
1.9.3 ICS unclear					

Favours control 0.1 0.2 0.5 1 2 5 10 Favours mucolytic



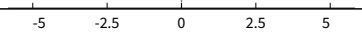
Analysis 1.10. Comparison 1 Mucolytic versus placebo, Outcome 10 Number of exacerbations per participant per month.

	Number of exacerbations per participant per month						
Study	Mean mucolytic group	SD	N	Mean control group	SD	N	Mean difference [95% CI]
Allegra 1996	0.07	0.11	223	0.11	0.14	218	-0.04 [-0.06, -0.02]
Babolini 1980	0.13	0.18	254	0.33	0.27	241	-0.20 [-0.24, -0.16]
Boman 1983	0.2	0.27	98	0.32	0.3	105	-0.12 [-0.20, -0.04]
Borgia 1981	0.05	0.08	10	0.15	0.17	9	-0.10 [-0.22, 0.02]
Castiglioni 1986	0.1	0.21	311	0.2	0.29	302	-0.10 [-0.14, -0.06]
Cremonini 1986	0.25	0.23	21	0.71	0.29	20	-0.46 [-0.62, -0.30]
Decramer 2005	0.1	0.11	256	0.11	0.16	267	-0.01 [-0.03, 0.01]
Fukuchi 2016	0.15	0.24	201	0.13	0.21	204	0.02 [-0.02, 0.06]
Grassi 1976	0.14	0.15	35	0.27	0.21	34	-0.13 [-0.22, -0.04]
Grassi 1994	0.16	0.29	42	0.45	0.43	41	-0.29 [-0.45, -0.13]
Grillage 1985	0.1	0.12	54	0.12	0.15	55	-0.02 [-0.07, 0.03]
Hansen 1994	0.11	0.15	59	0.16	0.19	70	-0.05 [-0.11, 0.01]
Jackson 1984	0.11	0.14	61	0.13	0.16	60	-0.02 [-0.07, 0.03]
Malerba 2004	0.06	0.08	115	0.07	0.08	119	-0.01 [-0.03, 0.01]
McGavin 1985	0.42	0.34	72	0.52	0.35	76	-0.10 [-0.21, 0.01]
Meister 1986	0.15	0.15	90	0.2	0.19	91	-0.05 [-0.10, -0.00]
Meister 1999	0.06	0.15	122	0.1	0.15	124	-0.04 [-0.08, -0.00]
Moretti 2004	0.12	0.14	63	0.17	0.17	61	-0.05 [-0.10, 0.00]
Nowak 1999	0.03	0.06	147	0.06	0.12	148	-0.03 [-0.05, -0.01]
Olivieri 1987	0.18	0.31	110	0.33	0.41	104	-0.15 [-0.25, -0.05]
Parr 1987	0.18	0.21	243	0.21	0.21	210	-0.03 [-0.07, 0.01]
Pela 1999	0.14	0.15	35	0.27	0.21	34	-0.13 [-0.22, -0.04]
Rasmussen 1988	0.13	0.21	44	0.14	0.19	47	-0.01 [-0.09, 0.07]
Schermer 2009	0.08	0.1	96	0.06	0.05	96	0.02 [-0.00, 0.04]
Tse 2013	0.08	0.24	58	0.14	0.24	62	-0.06 [-0.15, 0.03]
Worth 2009	0.067	0.136	110	0.15	0.24	110	-0.08 [-0.13, -0.03]
Zheng 2008	0.084	0.094	353	0.11	0.094	354	-0.03 [-0.04, -0.01]

Study	Number of exacerbations per participant per month						
	Mean mucolytic group	SD	N	Mean control group	SD	N	Mean difference [95% CI]
Zheng 2014	0.1	0.15	482	0.13	0.17	482	-0.03 [-0.05, -0.01]

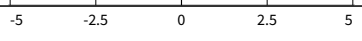
Analysis 1.11. Comparison 1 Mucolytic versus placebo, Outcome 11 Days of disability per participant per month.

Study or subgroup	Mucolytic		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Allegra 1996	171	0.6 (1.2)	181	1.1 (1.6)		18.19%	-0.49[-0.79,-0.19]
Bontognali 1991	30	4.6 (3.8)	30	7.9 (4.6)		0.36%	-3.27[-5.39,-1.15]
Cremonini 1986	20	0.6 (0.8)	21	2.5 (2.3)		1.57%	-1.99[-3.01,-0.97]
McGavin 1985	72	1 (1.4)	76	1 (1.9)		5.68%	-0.06[-0.59,0.47]
Olivieri 1987	110	0.7 (1.2)	104	1.3 (1.7)		10.7%	-0.65[-1.04,-0.26]
Pela 1999	85	1 (0.8)	84	1.3 (1.9)		8.5%	-0.3[-0.74,0.14]
Rasmussen 1988	44	1.4 (2.9)	47	2 (3.8)		0.86%	-0.55[-1.92,0.82]
Worth 2009	110	0.7 (1.8)	110	1 (1.5)		8.42%	-0.28[-0.72,0.16]
Zheng 2014	482	1.2 (1.2)	482	1.6 (1.8)		45.72%	-0.37[-0.56,-0.18]
Total * **	**1124**		**1135**			**100%**	**-0.43[-0.56,-0.3]**
Heterogeneity: Tau^2=0; Chi^2=20.37, df=8(P=0.01); I^2=60.73%							
Test for overall effect: Z=6.59(P<0.0001)							



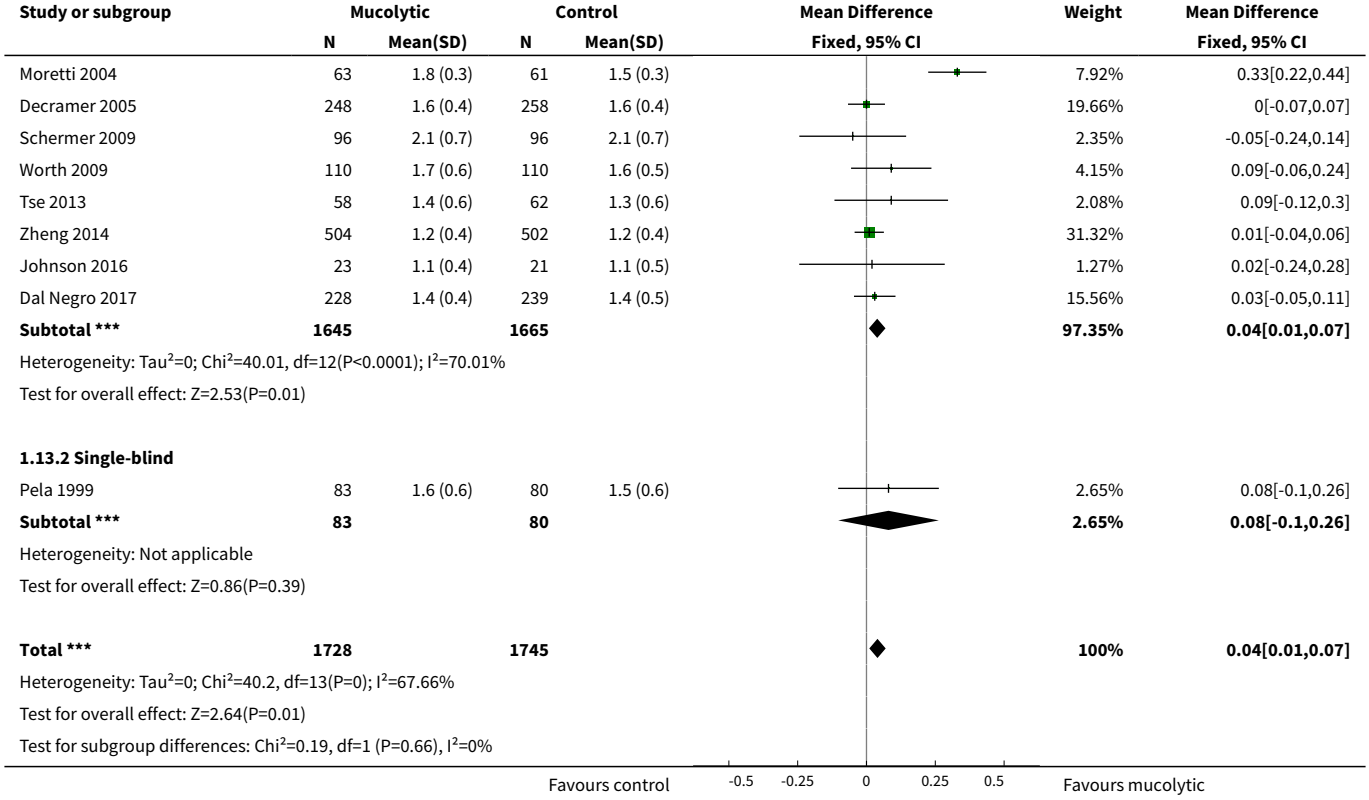
Analysis 1.12. Comparison 1 Mucolytic versus placebo, Outcome 12 Days on antibiotics per participant per month.

Study or subgroup	Mucolytic		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Allegra 1996	171	0.6 (1.2)	181	1.1 (1.5)		58.52%	-0.42[-0.71,-0.13]
McGavin 1985	72	2.7 (2.9)	76	3.6 (4.9)		2.97%	-0.9[-2.18,0.38]
Olivieri 1987	110	0.6 (1)	104	1.3 (1.6)		38.51%	-0.68[-1.04,-0.32]
Total * **	**353**		**361**			**100%**	**-0.53[-0.76,-0.31]**
Heterogeneity: Tau^2=0; Chi^2=1.55, df=2(P=0.46); I^2=0%							
Test for overall effect: Z=4.73(P<0.0001)							

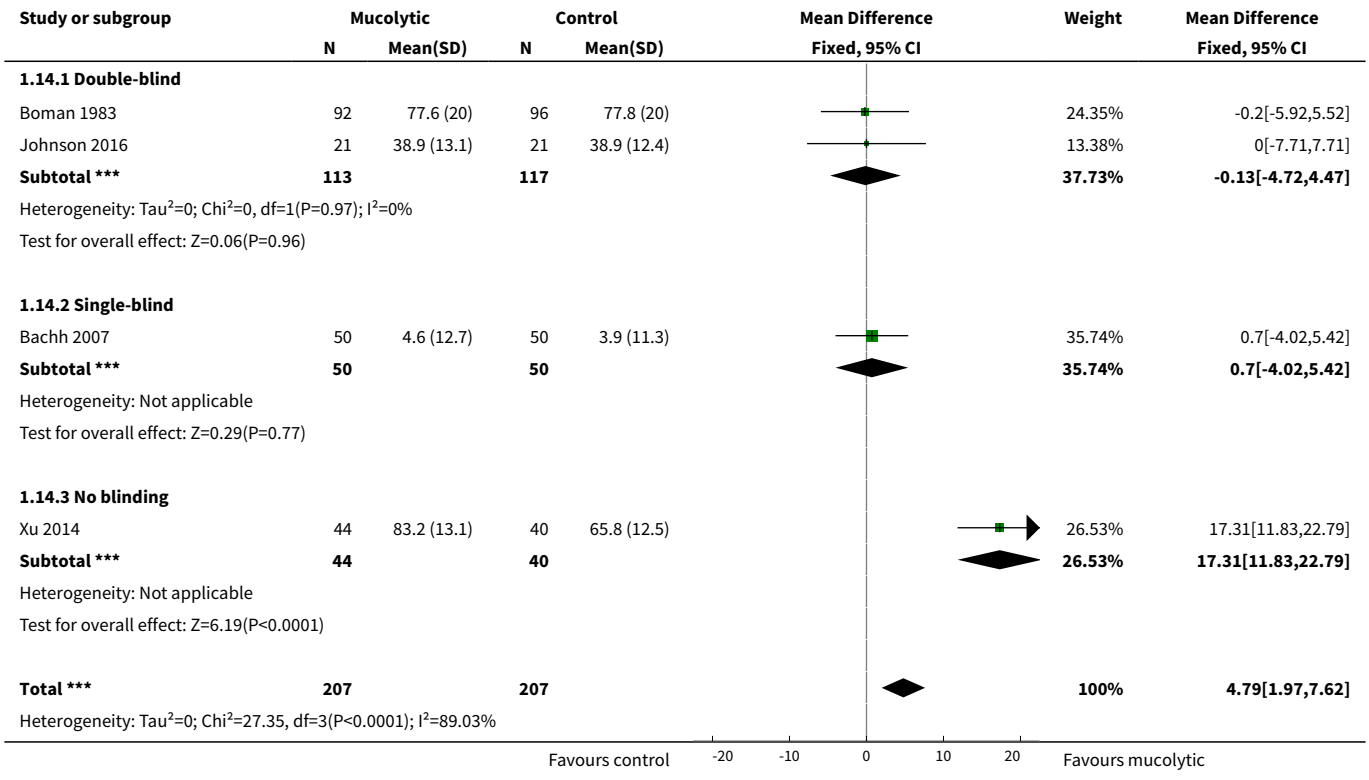


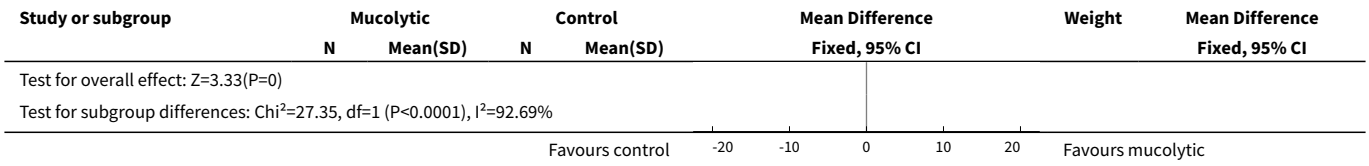
Analysis 1.13. Comparison 1 Mucolytic versus placebo, Outcome 13 FEV_1 at end of study.

Study or subgroup	Mucolytic		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
1.13.1 Double-blind							
Borgia 1981	10	3.5 (0.6)	9	3.1 (1.1)		0.13%	0.49[-0.34,1.32]
McGavin 1985	85	0.8 (0.4)	96	0.9 (0.4)		8.03%	-0.06[-0.16,0.04]
Olivieri 1987	104	1.9 (0.7)	94	1.9 (0.6)		2.77%	0.06[-0.12,0.24]
Cegla 1988	86	2.5 (0.8)	87	2.5 (0.8)		1.59%	0[-0.24,0.24]
Bontognali 1991	30	2.5 (0.8)	30	2.1 (0.8)		0.52%	0.35[-0.06,0.76]

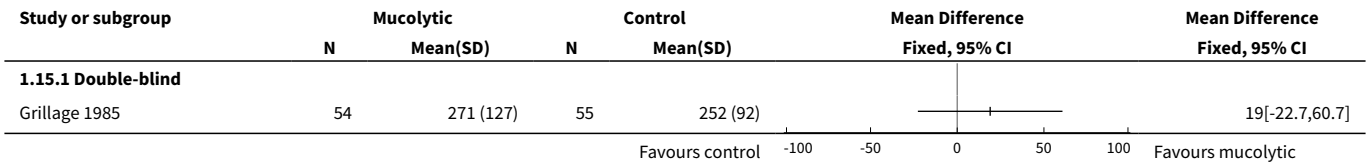


Analysis 1.14. Comparison 1 Mucolytic versus placebo, Outcome 14 Percent predicted FEV_1.

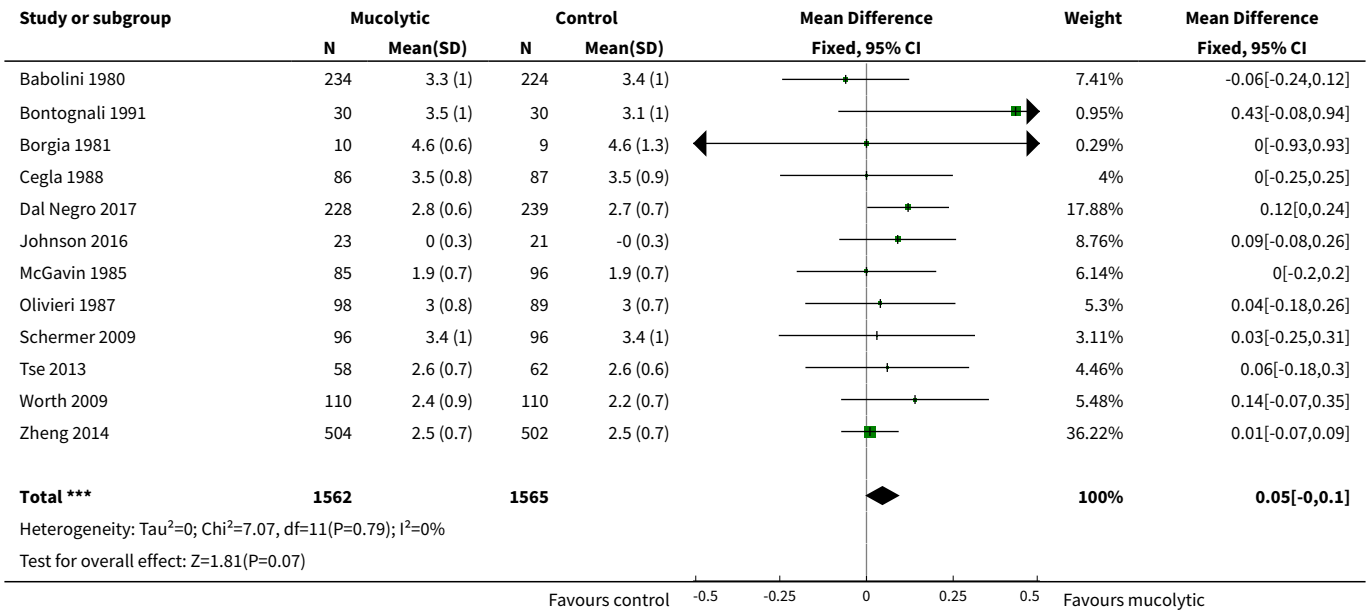




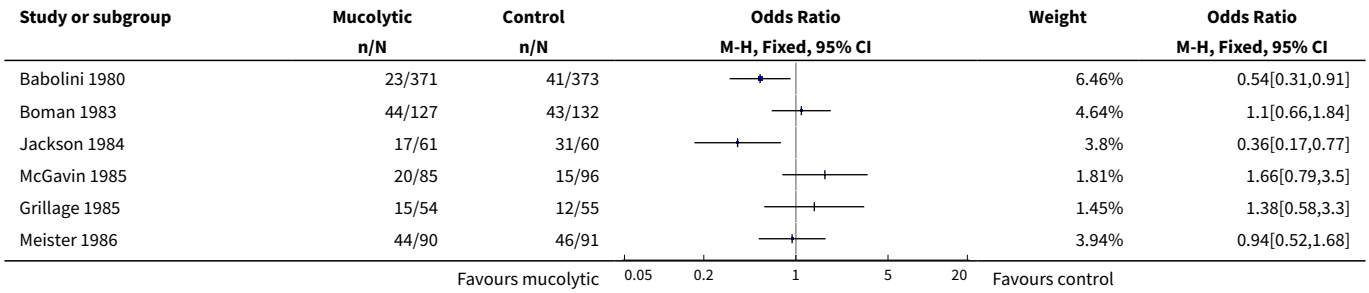
Analysis 1.15. Comparison 1 Mucolytic versus placebo, Outcome 15 PEFR at end of study.

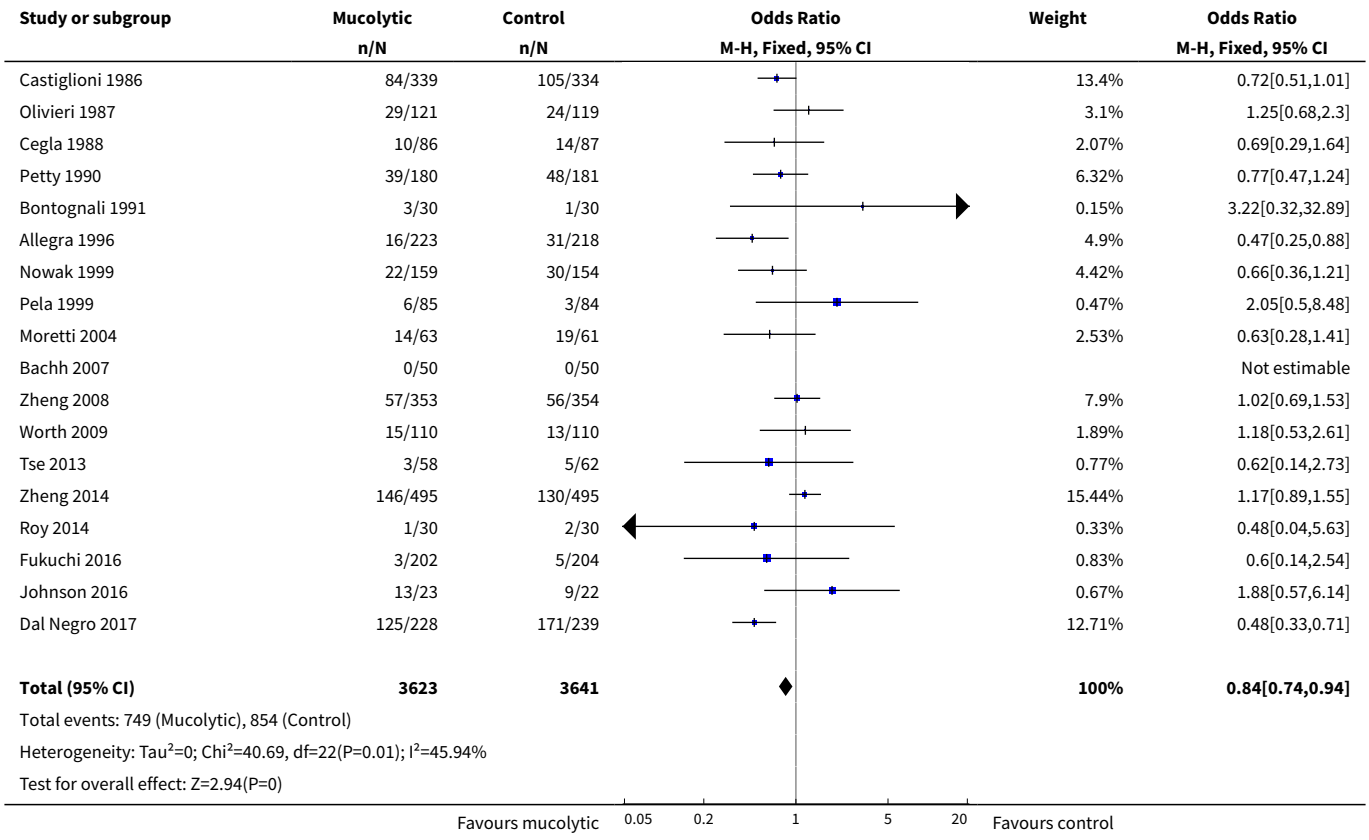


Analysis 1.16. Comparison 1 Mucolytic versus placebo, Outcome 16 FVC at end of study.

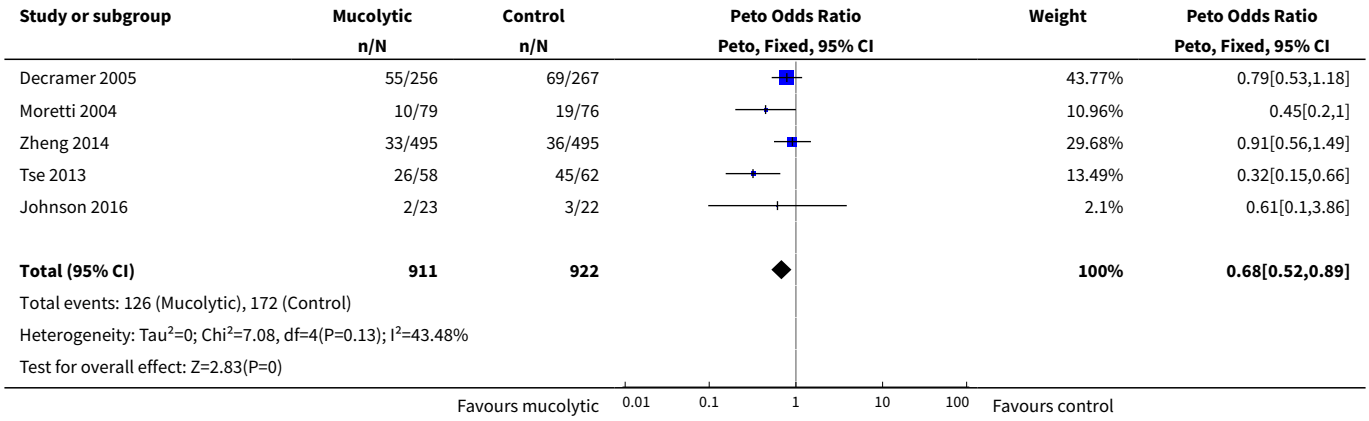


Analysis 1.17. Comparison 1 Mucolytic versus placebo, Outcome 17 Adverse effects.

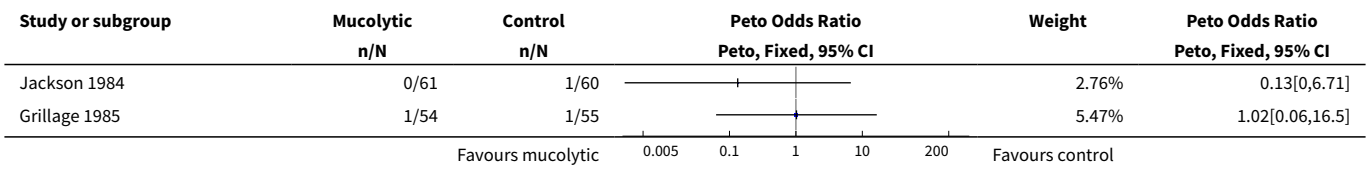




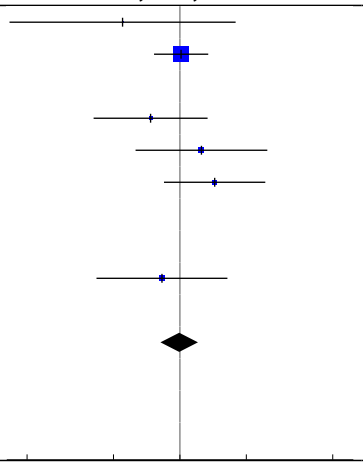
Analysis 1.18. Comparison 1 Mucolytic versus placebo, Outcome 18 Hospitalisation during study period.



Analysis 1.19. Comparison 1 Mucolytic versus placebo, Outcome 19 Death during study period.

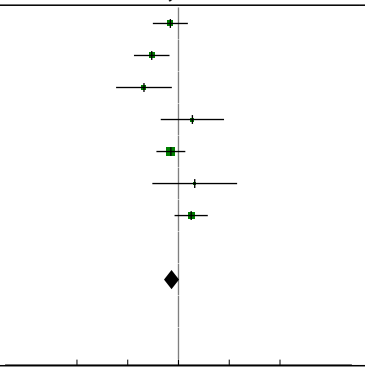


Study or subgroup	Mucolytic n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Pela 1999	0/84	1/85		2.76%	0.14[0,6.9]
Decramer 2005	9/256	9/267		48.04%	1.04[0.41,2.67]
Zheng 2008	0/353	0/354			Not estimable
Schermer 2009	1/96	3/96		10.87%	0.36[0.05,2.61]
Tse 2013	2/58	1/62		8.13%	2.11[0.22,20.71]
Zheng 2014	4/495	1/495		13.74%	3.34[0.58,19.33]
Xu 2014	0/44	0/40			Not estimable
Johnson 2016	0/23	0/22			Not estimable
Dal Negro 2017	1/228	2/239		8.24%	0.54[0.06,5.19]
Total (95% CI)	**1752**	**1775**		**100%**	**0.98[0.51,1.87]**
Total events: 18 (Mucolytic), 19 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.53, df=7(P=0.6); I^2=0%					
Test for overall effect: Z=0.07(P=0.94)					



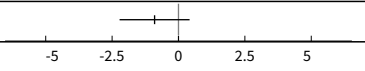
Analysis 1.20. Comparison 1 Mucolytic versus placebo, Outcome 20 Health-related quality of life (total score St. George's Respiratory Questionnaire).

Study or subgroup	Mucolytic N	Mucolytic Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Decramer 2005	165	34.7 (16)	146	36.3 (15)		18.46%	-1.6[-5.05,1.85]
Zheng 2008	305	37.5 (21.4)	311	42.8 (22.9)		17.91%	-5.27[-8.77,-1.77]
Worth 2009	110	34.5 (18.9)	110	41.3 (22.5)		7.27%	-6.8[-12.29,-1.31]
Tse 2013	58	28.5 (17.5)	62	25.8 (17.3)		5.65%	2.74[-3.49,8.97]
Zheng 2014	482	40 (22.1)	482	41.5 (23)		27.09%	-1.5[-4.35,1.35]
Johnson 2016	23	-3.9 (12.1)	22	-7.1 (16.1)		3.15%	3.2[-5.15,11.55]
Dal Negro 2017	215	39.9 (17.7)	230	37.4 (17.5)		20.47%	2.5[-0.77,5.77]
Total ***	**1358**		**1363**			**100%**	**-1.37[-2.85,0.11]**
Heterogeneity: Tau^2=0; Chi^2=16.75, df=6(P=0.01); I^2=64.17%							
Test for overall effect: Z=1.82(P=0.07)							



Analysis 1.21. Comparison 1 Mucolytic versus placebo, Outcome 21 Health-related quality of life (total score COPD Assessment Test).

Study or subgroup	Mucolytic N	Mucolytic Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Fukuchi 2016	171	-2.9 (6.3)	169	-2 (6.1)		0%	-0.9[-2.22,0.42]

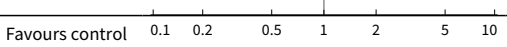


Comparison 2. Systemic thiol donor versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with no exacerbations in the study period	1	628	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.74, 1.39]
2 Number of exacerbations per participant per month			Other data	No numeric data
3 Days of disability per participant per month	1	628	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.82, 0.46]
4 Adverse effects	1	628	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.39 [0.98, 1.95]

Analysis 2.1. Comparison 2 Systemic thiol donor versus placebo, Outcome 1 Participants with no exacerbations in the study period.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Ekberg-Jansson 1999	174/313	174/315		100%	1.01[0.74,1.39]
Total (95% CI)	**313**	**315**		**100%**	**1.01[0.74,1.39]**
Total events: 174 (Treatment), 174 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.09(P=0.93)					

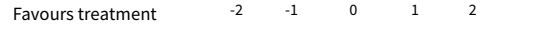


Analysis 2.2. Comparison 2 Systemic thiol donor versus placebo, Outcome 2 Number of exacerbations per participant per month.

Study	Number of exacerbations per participant per month: Mean mucolytic group	SD	N	Mean control group	SD	N	Mean difference [95% CI]
Ekberg-Jansson 1999	0.18	0.22	313	0.17	0.21	315	0.01 [-0.02, 0.04]

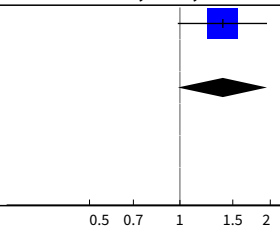
Analysis 2.3. Comparison 2 Systemic thiol donor versus placebo, Outcome 3 Days of disability per participant per month.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Ekberg-Jansson 1999	313	2.6 (4)	315	2.8 (4.2)		100%	-0.18[-0.82,0.46]
Total ***	**313**		**315**			**100%**	**-0.18[-0.82,0.46]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.55(P=0.58)							



Analysis 2.4. Comparison 2 Systemic thiol donor versus placebo, Outcome 4 Adverse effects.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Ekberg-Jansson 1999	231/313	211/315		100%	1.39[0.98,1.95]
Total (95% CI)	**313**	**315**		**100%**	**1.39[0.98,1.95]**
Total events: 231 (Treatment), 211 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.87(P=0.06)					



ADDITIONAL TABLES

Table 1. Summary of study characteristics

Study ID	Total n	Study duration (weeks)	Mean age (years)	COPD severity	Country	Intervention	Control	Outcomes
Allegra 1996	440	26	60.0	Moderate to severe	Italy	Carbocysteine-lysine 2.7 g daily	Placebo	Diary of scores, exacerbations, time to first exacerbation, duration of exacerbation, days on antibiotics, AEs
Babolini 1980	744	26	Not reported	Moderate to severe	Italy	NAC 200 mg twice daily	Placebo	Exacerbations, symptom scores, global assessments by patients and physicians, AEs, days on antibiotics
Bachh 2007	100	52	61.0	Moderate to severe	India	NAC 600 mg once daily	Placebo	Exacerbations, hospital admissions, lung function, AEs
Boman 1983	259	26	51.9	Severe to very severe	Sweden	NAC 200 mg twice daily	Placebo	Exacerbations, sick leave due to exacerbation, AEs
Bontognali 1991	60	13	57.0		Italy	Cithiolone 400 mg twice daily	Placebo for 1 month followed by 400 mg once daily for a further 2 months	Exacerbations, duration of acute exacerbations, FEV_1, FVC, sputum viscosity, AEs
Borgia 1981	21	26	45.3	Moderate to severe	Italy	NAC 200 mg twice daily	Placebo	Exacerbations, lung function, symptom scores, clinical assessments, AEs
Castiglioni 1986	706	13	56.5	Mild to moderate	Italy	Sobrerol 300 mg twice daily	Placebo	Exacerbation rate, consumption of antibiotics, clinical signs, laboratory data, lung function, global assessment by investigator and patient, AEs
Cegla 1988	180	104	51.1		Germany	Ambroxol retard 75 mg	Placebo	Exacerbations, days sick (off work, in hospital), patient symptoms by diary card, lung function, extra medication use, assessment by investigator and patient, AEs

Table 1. Summary of study characteristics *(Continued)*

Cremonini 1986	41	13	60.8		Italian	Letosteine 50 mg 3 times daily	Placebo	Exacerbations, days off sick, lung function
Dal Negro 2017	467	52	64.8	Moderate to severe	10 European countries	Erdosteine 300 mg twice daily	Placebo	Number of acute exacerbations, spirometry parameters, COPD symptoms, QoL, safety and tolerability of erdosteine
De Backer 2013	12	13	65.0	Moderate to severe	Belgium	NAC 600 mg 3 times daily	Placebo	Spirometry, PEFR, raw, NO, specific airway resistance from plethysmography, CT to look at airway geometry, serum glutathione, enzymes, SGRQ, ABG
Decramer 2005	523	156	62.0	Moderate to severe	Europe	NAC 600 mg daily	Placebo	Lung function, exacerbation rate, QoL, cost utility
Ekberg-Jansson 1999	637	26	58.0	Mild, moderate to severe	Europe	NIC 300 mg twice daily	Placebo	Time to first exacerbation, exacerbation rate, days sick (judged by patients and investigators), lung function, AEs
Fukuchi 2016	408	52	Not reported	Moderate, severe to very severe	Japan	Lysozyme 90 mg 3 times daily	Placebo	Exacerbation rate, time to first exacerbation, lung function, CAT
Grassi 1976	80	26	60.9		Italy	NAC 600 mg daily	Placebo	Exacerbations, clinical symptoms, sputum characteristics, AEs
Grassi 1994	135	13	61.8		Italy	Carbocysteine 1125 mg plus sobrerol 180 mg once daily	Placebo or alternating active-placebo for 10 days each	Exacerbations, symptoms, sputum characteristics
Grillage 1985	109	26	Not reported		Britain	Carbocysteine 750 mg 3 times daily	Placebo	Exacerbations, lung function, AEs
Hansen 1994	153	22	51.4	Mild to moderate	Denmark	NAC 600 mg twice daily	Placebo	Exacerbations, subjective symptom scores, global well-being, lung function, AEs

Table 1. Summary of study characteristics *(Continued)*

Jackson 1984	155	13	63.0		Great Britain	NAC 200 mg 3 times daily	Placebo	Exacerbations, subjective symptoms, clinical signs, radiological appearance, global well being, AEs
Johnson 2016	51	8	70.0	Mild to moderate	USA	NAC 1800 mg twice daily	Placebo	Change SGRQ, CBSAS, SF-36; post-bronchodilator lung function
Malerba 2004	242	52	60.0	Moderate	Italy	Ambroxol 75 mg twice daily	Placebo	Exacerbation over first 6 months (winter period) and at 12 months, cough intensity and frequency, difficult expectoration, dyspnoea, days on antibiotics, number of working days lost
McGavin 1985	244	22	63.4	Severe to very severe	Great Britain	NAC 200 mg 3 times daily	Placebo	Exacerbation, days of antibiotics, days in bed, FEV_1, VC, AEs
Meister 1986	252	26	57,2		Germany	NAC 300 mg twice daily	Placebo	Exacerbation, days sick, concomitant treatment, AEs
Meister 1999	246	26	57.0	Mild to moderate	Germany	Myrtol 300 mg 3 times daily	Placebo	Exacerbation, number of exacerbations requiring antibiotics, well-being, AEs
Moretti 2004	155	35	67.0	Moderate, severe to very severe	Italy	Erdosteine 300 mg twice daily	Placebo	Exacerbation frequency, duration, hospitalisation, lung function, 6MWT, SGRQ, pharmacoeconomic analysis
Nowak 1999	313	35	57.0		Europe	NAC 600 mg daily	Placebo	Exacerbation, severity of exacerbations, time to first exacerbation, days sick, lung function, patient symptoms, AEs
Olivieri 1987	240	26	Not reported	Mild, moderate to severe	Italy	Ambroxol retard 75 mg daily	Placebo	Exacerbation, course of antibiotics, days sick, FEV_1, VC, symptoms, auscultatory findings, physicians' and patients' global assessments, laboratory data, AEs
Parr 1987	526	26	63.0		Great Britain	NAC 200 mg 3 times daily	Placebo	Exacerbation, days off work, AEs
Pela 1999	169	26	66.0	Moderate, severe to very severe	Italy	NAC 600 mg daily	Placebo	Exacerbation, exacerbation severity, days sick, patient preference, lung function

Table 1. Summary of study characteristics *(Continued)*

Petty 1990	367	8	65.0	Moderate, severe to very severe	USA	Iodinated glycerol 30 mg 4 times daily	Placebo	Investigator assessment of symptoms, patient evaluation of symptoms and global assessment, frequency of bronchodilator use, number and duration of acute exacerbations, frequency of concomitant medications, AEs
Rasmussen 1988	116	26	58.9		Sweden	NAC 300 mg twice daily	Placebo	Exacerbation, days sick evaluated by days on sick list and by patient diaries, AEs
Roy 2014	80	26	61.0	Mild to Moderate	India	NAC 600 mg twice daily	Placebo	Symptoms (cough, dyspnoea, sputum), lung function, haemoglobin levels, AEs
Schermer 2009	192	156	59.0	Mild, moderate, severe to very severe	Netherlands	NAC 600 mg daily	Placebo	Rate of exacerbations, CRQ
Tse 2013	133	52	71.0	Mild, moderate to severe	China	NAC 600 mg twice daily	Placebo	Small airways parameters $FEF_{25-75\%}$, FOT, IC, spirometry, exacerbation rate, dyspnoea, SGRQ, 6MWD
Worth 2009	220	26	62.3	Moderate to severe	Germany	Cineole 200 mg 3 times daily	Placebo	Exacerbations: number, severity, and duration, lung function, dyspnoea, SGRQ, AEs
Xu 2014	84	26	Not reported	Moderate to severe	China	NAC 600 mg twice daily	Salmeterol/fluticasone propionate	FEV_1 %/FVC, FEV_1 % predicted, PEF% daily variation change, PaO_2, $PaCO_2$
Zheng 2008	709	52	65.0	Moderate, severe to very severe	China	Carbocysteine 500 mg 3 times daily	Placebo	Exacerbation rate, covariance-adjusted exacerbation rate, QoL, lung function, arterial oxygen saturation
Zheng 2014	1006	52	66.0	Moderate to severe	China	NAC 600 mg 3 times daily	Placebo	Exacerbation rate, exacerbation duration, time to first exacerbation, time to recurrent exacerbation, number of participants requiring systemic corticosteroids or antibiotics or SABA, SGRQ (Chinese version), lung function, AEs (including hospitalisation or death)

6MWD: six-minute walk distance; AEs: adverse events; CAT: COPD assessment test; CBSAS: Chronic Bronchitis Symptoms Assessment Scale; CRQ: chronic respiratory questionnaire; $FEF_{25-75\%}$: forced expiratory flow at 25%-75% of the pulmonary volume; FEV_1: forced expiratory volume in one second; FOT: forced oscillatory technique; FVC: forced vital capacity; IC: inspiratory capacity; NAC: N-acetylcysteine; NIC: N-isobutyrylcysteine; $PaCO_2$: partial pressure of carbon dioxide; PaO_2: partial pressure of oxygen; PEF: peak expiratory flow; QoL: quality of life; SABA: short-acting beta-agonist; SCMC-Lys: carbocysteine lysine salt monohydrate; SF-36:Short Form-36 Health Survey; SGRQ: St. George's respiratory questionnaire; VC: vital capacity.

APPENDICES

Appendix 1. Search history

Years	Search result detail
All years to January 1998	We screened approximately 400 abstracts of papers identified by computer searches. After excluding studies that were clearly ineligible based on the abstract, we obtained the full text for 72 papers. 21 studies involved double-blind, placebo-controlled treatment with an oral mucolytic for at least 8 weeks. 3 were excluded because they did not provide information on the primary outcome (Edwards 1976; Maesen 1980; Rubin 1996). Three studies were excluded because they did not report the standard deviation for outcome measures of interest, and we could not obtain this information despite writing to study authors (Christensen 1971; Grillage 1985; Jackson 1984). 15 studies were included in the review
January 1998 to 1999	For the 1999 update, one further study was identified that had been detected on the original search (Cegla 1988), but for which the full text had not been obtained in 1997. Grillage 1985 and Jackson 1984 were not included in the original review but were included in the update, as they had data on participants with no exacerbations - an outcome measure that was added for the update. For this update, and until further clarification is obtained from study authors, we have assumed that error measurement reported in Olivieri 1987 is an SE rather than an SD (see Lung Function)
January 1999 to 2002	In 2002, the search was widened to (chronic bronchitis or emphysema or chronic obstructive pulmonary disease or COPD) AND (mucolytics or mucoactive or N-acetylcysteine or bromhexine or S-carboxymethylcysteine or ambroxol or sobrerol or iodinated glycerol or N isobutyrylcysteine or myrtol or NAC or methylcysteine or carbocysteine or erdosteine or strepronin or gelsolin or MESNA). No further eligible studies were identified by this search
January 2002 to January 2003	In 2003, a repeat search with the same terms yielded 44 titles, of which 18 abstracts were screened for eligibility and 5 full texts were retrieved; none were eligible
January 2003-Sept 2005	An update search conducted in 2005 yielded another 264 titles, of which 9 full texts were retrieved, yielding a further 3 studies for inclusion (Decramer 2005; Malerba 2004; Moretti 2004).
2005-2007	A search in 2005 yielded another 16 titles, none of which were eligible; in 2006, a further 2 titles were found with the COOPT study eligible
2008	Searches in 2008 yielded 20 titles, with 2 more original studies for inclusion (Bachh 2007; Zheng 2008)
May 2011	In 2011, 64 abstracts and papers were identified by the searches. Several reports were related to the PEACE study (Zheng 2008), and to the EQUALIFE study already included in this review (Moretti 2004). Of 7 full texts reviewed, 4 proved eligible: 2 related to the same study of cineole in COPD (Worth and Worth); another to a further study of cineole (Wilhelmi); one was a further post hoc analysis of EQUALIFE (Ballabio 2008a). One study (Lukas) of NAC in CB was excluded, as no data were available on outcomes in this review Furthermore, we were informed about studies of neltenexine, which is a mucolytic, and we considered the full texts of these, which were ineligible. Thus data from 2 new studies were added for the 2012 update (mucolytic* or "mucociliary clearance" or mucoactive or N-acetylcysteine or bromhexine or S-carboxymethylcysteine or ambroxol or sobrerol or "iodinated glycerol" or N isobutyrylcysteine or myrtol or NAC or methylcysteine or carbocysteine or erdosteine or strepronin* or gelsolin or MESNA) In 2011, the above search was run from 2008 to the present date, but with the addition of the term "cineole". We were notified about eligible studies of "neltenexine". This term should be included in the next search

(Continued)

July 2012	In 2012, 8 abstracts and papers were identified. An abstract was added to "Studies awaiting classification" (Moretti 2011a)
July 2014	A search in July 2014 using the terms below yielded 29 new references (The full search strategy used in this update is provided in Appendix 3) Full texts of studies that were possibly eligible were retrieved. The Moretti trial mentioned above was ineligible. Several studies had duplicate reports. A search was made of the bibliographies of eligible studies, as well as of online clinical trials. A duplicate paper on a trial already identified was found during a search for study author details. From these searches, 4 new eligible trials were identified for inclusion in this review (De Backer 2013; Roy 2014; Tse 2013; Zheng 2014). We wrote to Dr De Backer to request additional information on the secondary outcomes of SGRQ and spirometry alluded to in their paper, with no response. Dr Zheng provided further information on several outcomes (Zheng 2014)
July 2017	A database search yielded 54 references, and searches of clinical trial registries identified a further 13 records. We excluded 50 on the basis of title and abstract and reviewed 17 full texts for possible inclusion. We excluded a further six records (5 unique studies) at this stage and identified 1 ongoing study that meets the inclusion criteria for this review. The remaining 10 records were eligible for inclusion. Six records, linked to 4 new unique studies, were added to the review (Dal Negro 2017; Fukuchi 2016; Johnson 2016; Xu 2014). A further 4 records identified were additional references to studies already included in the review

Appendix 2. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Dates searched	Frequency of search
CENTRAL (via the Cochrane Register of Studies (CRS))	From inception	Monthly
MEDLINE (Ovid)	1946 onwards	Weekly
EMBASE (Ovid)	1974 onwards	Weekly
PsycINFO (Ovid)	1967 onwards	Monthly
CINAHL (EBSCO)	1937 onwards	Monthly
AMED (EBSCO)	From inception	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards

(Continued)

Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the Cochrane Airways Trials Register

COPD search

1. Lung Diseases, Obstructive/

2. exp Pulmonary Disease, Chronic Obstructive/

3. emphysema$.mp.

4. (chronic$ adj3 bronchiti$).mp.

5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.

6. COPD.mp.

7. COAD.mp.

8. COBD.mp.

9. AECB.mp.

10. or/1-9

Filter to identify RCTs

1. exp "clinical trial [publication type]"/

2. (randomised or randomised).ab,ti.

3. placebo.ab,ti.

4. dt.fs.

5. randomly.ab,ti.

6. trial.ab,ti.

7. groups.ab,ti.

8. or/1-7

9. Animals/

10. Humans/

11. 9 not (9 and 10)

12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases

Appendix 3. Search strategy to identify relevant trials from the Cochrane Airways Trials Register

Search platform: Cochrane Register of Studies (CRS)

#1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All

#2 MeSH DESCRIPTOR Bronchitis, Chronic

#3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)

#4 COPD:MISC1

#5 (COPD OR COAD OR COBD):TI,AB,KW

#6 #1 OR #2 OR #3 OR #4 OR #5

#7 MeSH DESCRIPTOR Expectorants

#8 mucolytic*

#9 mucociliary* NEXT clearance*

#10 mucoactive

#11 *acetylcysteine

#12 bromhexine

#13 *carboxymethylcysteine

#14 ambroxol

#15 sobrerol

#16 "iodinated glycerol"

#17 isobutyrylcysteine

#18 myrtol

#19 NAC:ti,ab

#20 methylcysteine

#21 carbocysteine

#22 erdosteine

#23 strepronin*

#24 gelsolin

#25 mesna*

#26 cineole

#27 neltenexine

#28 eucalyptus

#29 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28

#30 #6 and #29

[Note: in search line #4, MISC1 denotes the field in which the reference has been coded for condition, in this case, COPD]

FEEDBACK

Incorrect dose reported in Zheng 2014 study, 13 February 2020

Summary

In reading the 2019 update to "Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease," I noticed that the N-acetylcysteine (NAC) dose in Zheng 2014 was reported as 1800 mg. In reading the published PANTHEON study, the intervention of NAC was 600 mg twice daily which would put it in the 1200 mg per day subgroup. Could you please comment on the dose? Thank you.

Reference: Zheng JP, Wen FQ, Bai CX, et al.PANTHEON study group. Twice daily N-acetylcysteine 600 mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON): a randomised, doubleblind placebo-controlled trial. Lancet Respir Med. 2014 Mar;2(3):187-94. doi: 10.1016/S2213-2600(13)70286-8

Reply

We thank the reader Kathy Grams very much for her interest in our review and for taking the time to give feedback, which in this case corrects an error.

We had indeed recorded the N-acetylcysteine (NAC) dose in the PANTHEON study by Zheng et al. 2014 as 1800 mg. It is in fact 1200 mg, being 600 mg twice daily. As a result of this we have made the following changes:

1. Corrected the dose in the Characteristics of included studies table
2. Corrected text describing included studies
3. In Analysis 1.4 moved Zheng from the 1800 mg subgroup to the 1200 mg subgroup.
4. Minor change to text describing this result.

While there are no changes to the overall findings of the review, we appreciate getting the information in the review as correct as possible.

Contributors

Feedback contributor: Kathy Grams, PharmD, BCGP

Author contributor: Phillippa Poole on behalf of the author team.

WHAT'S NEW

Date	Event	Description
9 March 2020	Feedback has been incorporated	Authors made changes to the reporting of one of the studies in the review. See Feedback 1. There were no changes to the overall findings of the review.
9 March 2020	Amended	Feedback added.

HISTORY

Protocol first published: Issue 2, 1996
Review first published: Issue 4, 1998

Date	Event	Description
23 April 2019	New search has been performed	• New literature search performed
23 April 2019	New citation required and conclusions have changed	• Change in review author team • Inclusion of 4 new studies (Dal Negro 2017; Fukuchi 2016; Johnson 2016; Xu 2014) • Removal of meta-analysis of outcome exacerbations per participant per month for methodological reasons

Date	Event	Description

		• Lung function outcomes separated into FEV_1, FEV_1 % predicted, PEFR, and FVC
		• ICS allowed vs ICS not allowed subgrouping amended
		• Conclusions for primary outcomes unchanged
		• Conclusions for secondary outcomes strengthened:
		  ◦ Increased certainty that mucolytics do not have an important impact on quality of life or lung function
		  ◦ Increased certainty that mucolytics are well tolerated

3 July 2014	New citation required but conclusions have not changed	• Change in review authors
		• Inclusion of 4 new studies, all of NAC vs placebo (De Backer 2013; Roy 2014; Tse 2013; Zheng 2014)
		• Addition of an analysis of studies lasting 12 months or longer
		• Addition to subgroup analysis of NAC at higher doses (1200 mg/d and 1800 mg/d)
		• For primary outcomes, minimal changes - all heading towards null effect, despite increased doses of NAC
		  ◦ Slightly reduced likelihood of no exacerbations during study period
		  ◦ Slightly reduced effect size for exacerbation rate
		• Addition of evidence of 'lack of effect' for all secondary outcomes
		• Addition of 'Summary of findings' table
		• Updated versions of 'Risk of bias' tables

3 July 2014	New search has been performed	New literature search
5 July 2012	New search has been performed	2 new studies (Worth 2009 (cineole) and Schermer 2009 (N-acetylcysteine (NAC)) included. Data from these studies and from Decramer 2005 included in a new analysis for SGRQ (St George Respiratory Questionnaire). 'Summary of findings' table added. Third review author (CC) added to the review. Potentially eligible abstract added to Studies awaiting classification
5 July 2012	New citation required and conclusions have changed	Conclusions similar, although smaller beneficial effects of mucolytics on exacerbations noted in more recent trials than in earlier trials
1 November 2008	New citation required but conclusions have not changed	Review updated to take account of 2 new studies
15 September 2008	New search has been performed	Search rerun
8 August 2008	Amended	Converted to new review format
10 March 2006	New citation required and conclusions have changed	2005: search repeated, full update performed. Three new studies, including 3-year BRONCHUS study of 600 mg NAC, included. Smaller effect size of all mucolytics combined than previously. Reasons for this discussed In the BRONCHUS study, significant effect of NAC on exacerbations noted among participants not using inhaled corticosteroids. New comparison added to address this Other new comparisons added: hospitalisations, deaths

Date	Event	Description
		Otherwise, findings much the same as previously
1 August 2002	New search has been performed	2002: no new studies found despite use of wider search strategy. Discussion expanded to include information on other recent meta-analyses of NAC and a comparison of the effects of mucolytics and fluticasone on exacerbations. Jadad scores for studies now included Data and conclusions same as in 1999
31 August 1999	New search has been performed	1999: 2 studies in patients with COPD now included in the review, hence the title change. Data on 2 other agents - myrtol and the thiol donor N-isobutyrylcysteine - also included. Eight additional studies and several new analyses included Correction made to reviewers' conclusions on the effects of mucolytics on the secondary endpoint of lung function. Our extracted data checked against original data and confirmed as correct. Small standard deviations in the Olivieri study noted; possibility that study authors reported standard errors. P values quoted in study analysis compatible with this conclusion. Until clarification, this trial removed from analysis. No significant change in lung function noted in data analysis (previously interpreted as favouring placebo). Changes made to relevant parts of Abstract, Results (Lung Function), and Discussion sections No change to overall conclusions of this review with respect to primary endpoint of exacerbation frequency and days of disability ('sick days'). High level of heterogeneity in the size of this effect between trials unclear; possibility that length of study is the cause of this should be examined in a future version of this review For adverse effects, Parr and Rasmussen data taken out of meta-analysis and reported instead in text because event rates in these studies exceeded numbers in treatment groups. RevMan unable to manage dichotomous data when event rate exceeds 1. Possibility that adverse effects may be less frequent in the mucolytic-treated group as suggested by meta-analysis. In large study by Parr (n = 526), mean of 4.9 adverse effects reported per participant in the mucolytic group vs 4.5 adverse effects per participant in the placebo group. Therefore, no changes made to our original conclusion and no differences between treatments in terms of adverse effects

CONTRIBUTIONS OF AUTHORS

Dr Phillippa Poole has had the primary overall responsibility for this review throughout its iterations. Until his death in 2010, Dr Black contributed to all aspects of the review, including approval of the final version of the substantive updates in 1999, 2002, 2005, 2006, and 2008. Dr Chris Cates has provided support for the review from inception. He has assisted with analysis, interpretation, data-checking, and write-up of the 2012 and 2014/15 updates. Dr Jimmy Chong assisted with determining study eligibility, checking data, and writing up the 2012 and 2014/15 updates. Dr Rebecca Fortescue and Kavin Sathananthan joined the team for the 2019 update and contributed to data extraction and entry and write-up. Dr Jimmy Chong and Dr Chris Cates stepped down from the author line for this most recent update.

Contributions of editorial team

Chris Cates (Co-ordinating Editor) checked the data entry before the full write-up of the review.
Sally Spencer (Editor) edited the review; advised on methodology, interpretation, and content; and approved changes after peer review.

Emma Dennett (Managing Editor) co-ordinated the editorial process; advised on interpretation and content; and edited the review.
Emma Jackson (Assistant Managing Editor) conducted peer review; and edited the plain language summary and reference sections of the protocol and the review.
Elizabeth Stovold (Information Specialist) designed the search strategy; ran the searches; and edited the search methods section.
Sarah Hodgkinson (Associate Editor, Cochrane Circulation and Breathing Network) screened the review and provided feedback.

DECLARATIONS OF INTEREST

PP: none known. I am an editor with Cochrane Airways.

KS: none known.

RF: none known. I am Joint Co-ordinating Editor of Cochrane Airways, employed by an NIHR grant, and a qualified general practitioner.

SOURCES OF SUPPORT

Internal sources

- No support received, Other.
- The authors declare that no such funding was received for this systematic review, Other.

External sources

- The authors declare that no such funding was received for this systematic review, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We searched trial registries for the update.

This review has used a modified version of the full 'Risk of bias' tool described in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions. The protocol and initial review versions used Jadad scores to assess trial quality. We have updated the 'Risk of bias' assessment to use the latest version of the Cochrane 'Risk of bias' tool.

Additional outcomes were added for updates from 2006 to 2012.

- Hospitalisation and mortality (added as outcomes for the 2006 and 2008 updates).
- Quality of life (added for the 2008 update, with a meta-analysis of SGRQ scores included for the 2012 update).

Double-blinding was not an inclusion criterion.

For the 2019 update, we removed the exacerbations per patient per month analyses, as these are not considered to be as statistically robust as the dichotomous exacerbation outcome, largely due to likely skew in this measure. In addition, we reviewed the Bontognali 1991 data for this outcome and removed them due to discrepancies in Table II of the publication, leading us to believe there are mistakes in the reported exacerbation data. Furthermore, following editorial advice, we conducted a sensitivity analysis while removing those studies judged to be at high risk of attrition bias.

INDEX TERMS

Medical Subject Headings (MeSH)

Bronchitis, Chronic [*drug therapy] [prevention & control]; Disease Progression; Expectorants [*therapeutic use]; Pulmonary Disease, Chronic Obstructive [*drug therapy] [prevention & control]; Quality of Life; Randomized Controlled Trials as Topic; Treatment Outcome

MeSH check words

Humans